NON-FELKIN DIASTEREOSELECTIVITY IN ALDOL COUPLINGS OF THIOPYRAN-BASED POLYPROPIONATE SYNTHONS

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By

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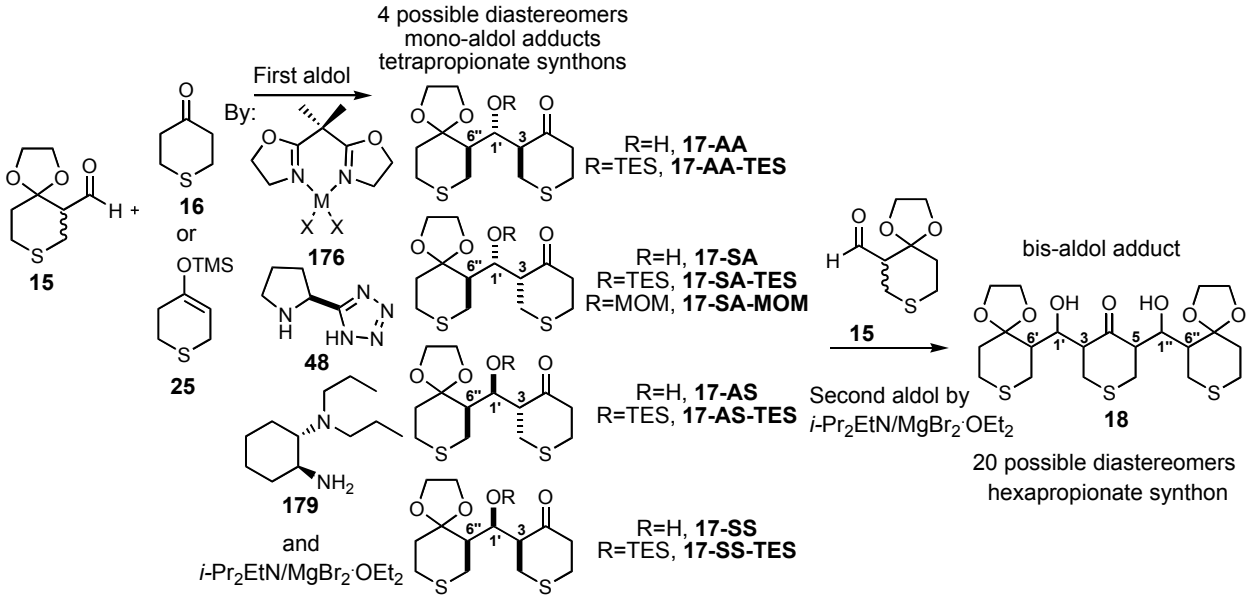
Abstract

Polypropionates represent a large family of natural products and several strategies have been developed for their synthesis. The aldol reaction is one of the most important tools for the construction of polypropionate natural products. The Ward group has developed an approach to polypropionate natural products based on sequential aldol reactions of thiopyran building blocks. The Thiopyran Route to Polypropionates (TR2P) involves the stepwise aldol reactions of **15** and **16** to rapidly access stereochemically complex tetrapropionate and hexapropionate synthons in a few steps. The current work describes the effort to prepare enantioenriched **17-AA** and/or **17-SA** through chiral transition metal based Lewis acids (**176**) and chiral organocatalysts (**48**, **179**) with chelating Lewis acids. The preparation of non-Felkin tetrapropionate and hexapropionate synthons through the use of a weak base in conjunction with a Lewis acid was developed.



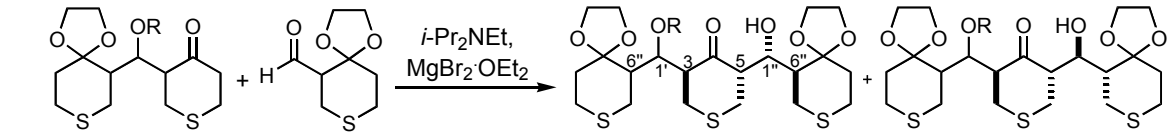
In section 2.1, the application of bis(oxazoline) ligands to the aldol reaction of **15** with **25** is discussed. Complexes with metal salts of bis(oxazoline) ligands (**176**) are unable to catalyze any aldol reaction between **15** and **25**. Other Lewis acidic transition metal salts without any ligands were also tried; however none could catalyze the aldol reaction between **15** and **25**.

In section 2.2, a modification of the (S)-5-(pyrrolidin-2-yl)tetrazole (**48**) catalyzed reaction is presented. After optimization efforts, the diastereoselectivity could not be improved to make the **17-AA** as the major adduct formed.

In section 2.3, the novel trans-*N*,*N*-dialkylated diaminocyclohexane catalyst (**179**) was applied to the aldol reaction of **15** and **16**. In all cases, the enantioselectivity and yield was low and it was determined that the catalyst was simply acting as a base and deprotonating ketone **16** to form the magnesium enolate.

Section 2.4 describes the use of a weak base in combination with a Lewis acid for mono-aldol formation. The $MgBr_2 \cdot OEt_2$ promoted aldol reaction of **15** and **16** was studied. The results show that the $MgBr_2 \cdot OEt_2$ and *i*-Pr_2EtN promoted aldol reaction of aldehyde **15** and ketone **16** can produce the non-Felkin adducts as a 2.2:1 mixture of **17-SA** and **17-AA** respectively in 70% yield.

After exploration of the $MgBr_2 \cdot OEt_2$ promoted aldol reaction of **15** with **16**, the $MgBr_2 \cdot OEt_2$ and *i*-Pr_2EtN promoted aldol reaction is applied to the aldol reaction of **15** with **17** and these results are presented in section 2.5. Reactions of **17-SA-TES**, **17-AA-TES**, **17-SA-MOM, 17-AS-TES** and **17-SS-TES** with **15** are highly diastereoselective: only 2 of 8 possible diastereomers are detected in moderate yield. After deprotection of the MOM and TES groups, three (**18-SA-trans-SA**, **18-SA-trans-AA**, and **18-AA-trans-AA**) of the previously unknown six bis-aldol diastereomers of **18** are available via this route. The cis-substituted bis-aldols adducts (**18-SA-cis-SA**, **18-SA-cis-AA**, and **18-AA-cis-AA**) are obtained through isomerization.



In section 3.6, the relative configuration of aldol diastereomers of **18** are determined using NMR methods, chemical synthesis (deprotection, reduction) and X-ray techniques.

Acknowledgements

I would like to acknowledge first and foremost, the unconditional support and encouragement I received from my family. Coolette and "G"-rant, this milestone could not have been achieved without your unwavering support. To my partners in crime Jason and Jessica, thank-you for ensuring there is never a dull moment; through the good times and the bad, you stood by my side and I am forever grateful. Baba, you hold a special spot in my heart and I want to thank you for always being there for me. To my extended family, I cannot thank you enough for your encouragement.

I would like to thank the department of Chemistry and the University of Saskatchewan for the opportunity to pursue my education in Saskatchewan. I would like to thank my research supervisor Dr. Dale Ward for welcoming me into his lab and for his support on this research project. The feedback provided by Dr. Michel Gravel and Dr. Dimmock was greatly appreciated. I thank all of my educators for their participation in my pursuit of education.

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To my friends who are there to celebrate the highs and the lows, the next round is on me!

To everyone who has offered me advice, encouragement, and friendship, I thank you. Your support, not only for this degree but also in life, is priceless.

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List of Abbreviations

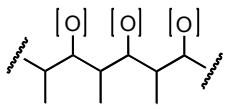
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOX	bis(oxazoline)
Bt	benzotriazole-3-yl
Bu	butyl
^{13}C NMR	carbon nuclear magnetic resonance
conc	concentrated
d	day(s)
i-Pr_2NEt	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
equiv	equivalent(s)
^{1}H NMR	proton nuclear magnetic resonance
h	hour(s)
HPLC	high performance liquid chromatography
IBX	2-iodoxybenzoic acid
M	molar

m-CPBA	meta-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
min	minute(s)
MOM	methoxymethyl
Pfp	pentafluorophenyl
PG	protecting group
Ph	phenyl
PhMe	toluene
PTSA	*para*-toluenesulfonic acid
rt	room temperature
t-Bu	*tert*-butyl (1,1-dimethylethyl)
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TR2P	thiopyran route to polypropionates
quant	quantitative

1. INTRODUCTION

1.1. Polypropionates and the Thiopyran Route to Polypropionates

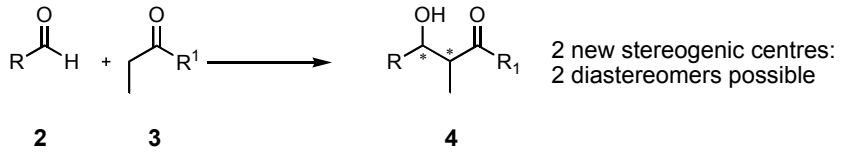
The synthesis of naturally occurring compounds by chemical methods has prompted the development of methodologies to access these often synthetically challenging structures.[1] Polyketides are a large class of natural products that are formed from the stepwise condensation of acetate units derived from the building block acetyl co-enzyme A. Polypropionates are a subgroup of polyketides that is characterized by a carbon chain with alternating methyl and oxygen (hydroxy or oxo) functionalities (Scheme 1).[1] This characteristic sequence is often part of a larger structure but is a major contributor to the stereochemical complexity of this class of natural products. Polypropionates are interesting synthetic targets due to their structural complexity and diverse biological activities including showing cytotoxic, antibiotic, antifungal and antiviral properties.[2] Many synthetic methods have been developed to access these complex natural products including reductive couplings, crotylations, allenylations, selective radical processes, sequential substitution, epoxide openings, rearrangement and intramolecular approaches.[1] The aldol reaction is one of the most important tools for the construction of polypropionate natural products. Versatile stereochemical control in aldol reactions is possible due to recent advances in aldol methodology. Specifically, modern aldol methods for the total synthesis of polyketides include a variety of metal enolates (lithium, titanium, boron, tin enolates), Lewis acid and base catalyzed aldol reactions, aldol reactions catalyzed by organocatalysts as well as aldol reactions catalyzed by enzymes (biocatalytic).[3]



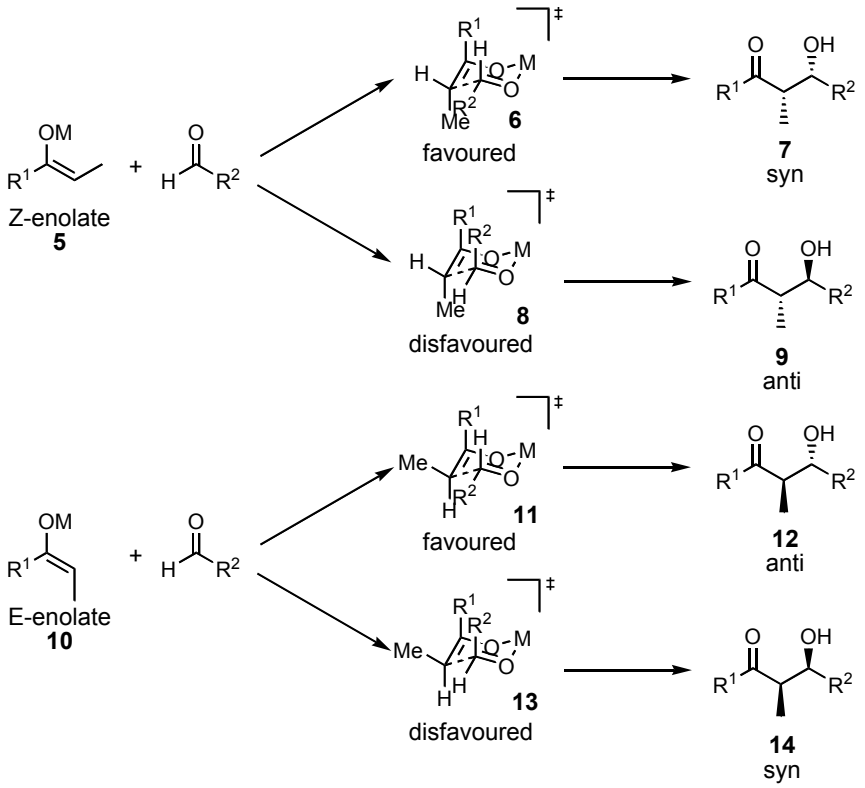
1

Scheme 1. Characteristic sequence of polypropionates **1**.

The aldol reaction is a versatile and widely used reaction to install the alternating oxo and methyl functionalities present in polypropionates (Scheme 2). Many factors influence the relative topicity (i.e. anti or syn relative configuration) of the aldol reaction. The nature of the enolate donor has a large effect. In general, *Z*-enolates give *syn* aldols and *E*-enolates give *anti* aldols predominantly. Zimmerman and Traxler proposed a model to account for these observations.[4] The Zimmerman-Traxler transition state model suggests intramolecular coordination of the aldehyde to the metal cation of the enolate, resulting in a closed six-membered ring chairlike transition state. The stereoselectivity of the reaction is governed by minimization of the 1,3-diaxial interactions between R^1 and R^2 in **6** versus **8**, and **11** versus **13**, which leads to the observed relative topicity (Scheme 3).



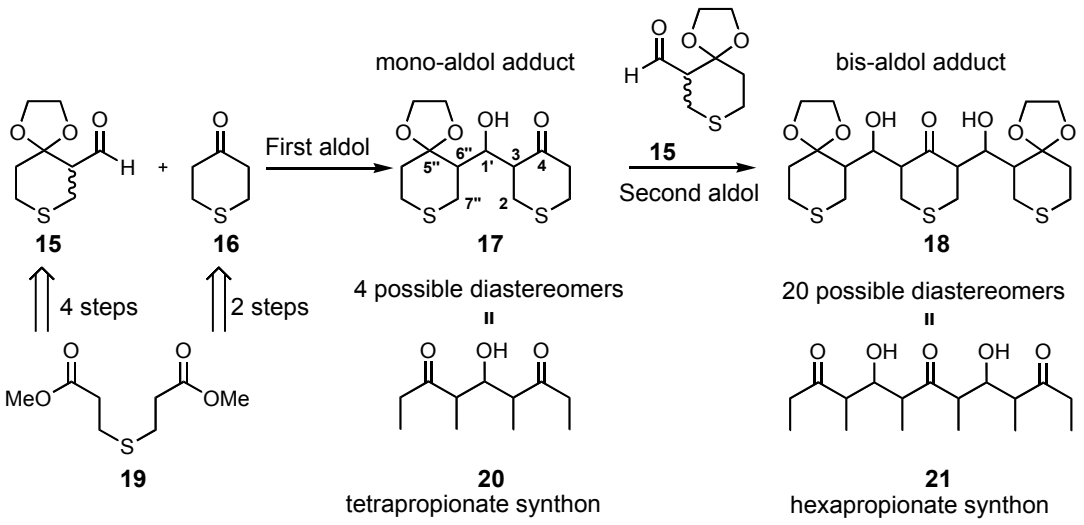
Scheme 2. Propionate aldol reaction.



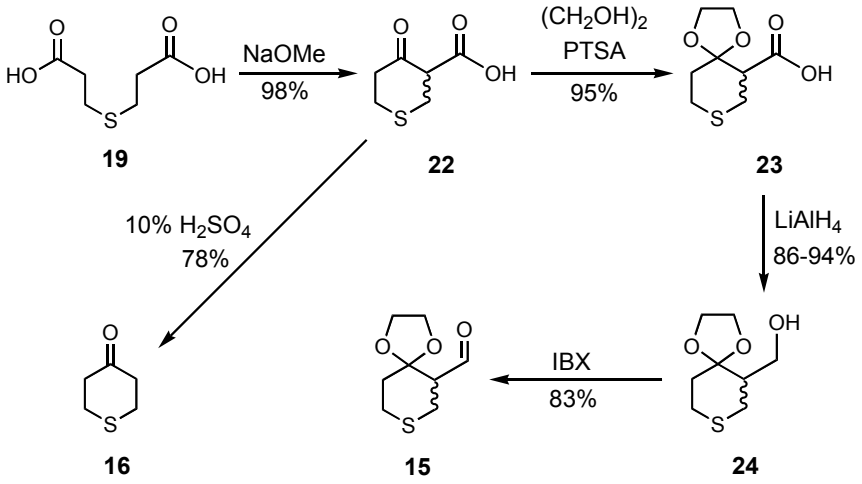
Scheme 3. Zimmerman-Traxler transition state model for addition of a metal enolate to an aldehyde.

The Ward group has developed an approach to polypropionate natural products based on sequential aldol couplings of thiopyran building blocks (Scheme 4).[5-13] Central to this strategy is the ability to control the stereochemical outcome of aldol couplings of inexpensive and easy to access starting materials **15** and **16** (Scheme 4). An aldol reaction of **15** and **16** produces the tetrapropionate synthon **17** (mono-aldol adduct) where 4 possible diastereomers can be produced. A second aldol reaction of **15** with **17** generates the hexapropionate synthon **18** (bis-aldol adduct) where 20 diastereomers are possible.

Both aldehyde **15** and ketone **16** are accessible from the common reagent dimethyl 3,3'-thiobispropanoate **19** on multigram scale in 4 and 2 steps, respectively (Scheme 5).[6, 7]



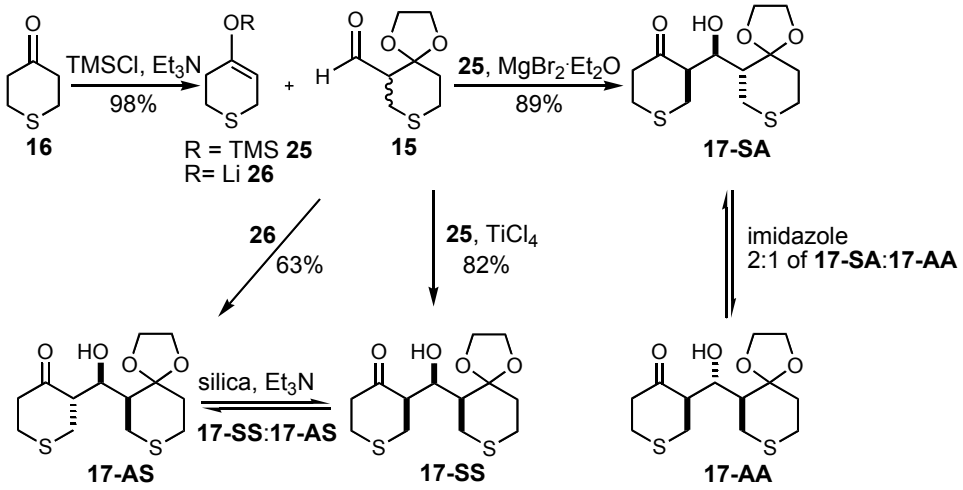
Scheme 4. Thiopyran Route to Polypropionates Synthetic Strategy.



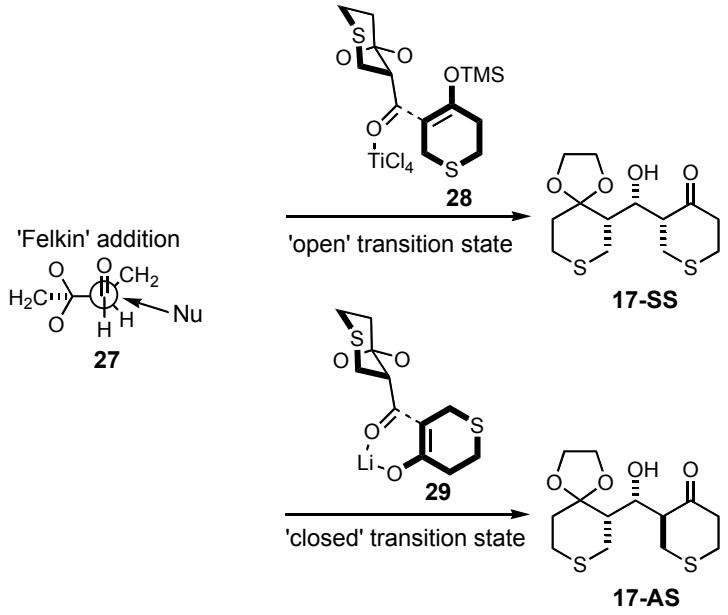
Scheme 5. Synthesis of building blocks **15** and **16**.

The Thiopyran Route to Polypropionates (TR2P) involves stepwise aldol reactions of **15** and **16** to rapidly access stereochemically complex polypropionate synthons in a few steps.[6, 7] Access to all four diastereomers of the first aldol reaction from the same starting materials is possible by varying the reaction conditions (Scheme 6).[7, 8] **17-AS** is synthesized via the 'amine-free' lithium enolate of **16** proceeding through a closed transition state and Felkin addition to chiral aldehyde **15** (Scheme 7). **17-SS** is synthesized through a Mukaiyama type aldol reaction of **26** with **15** promoted by the Lewis acid $TiCl_4$ proceeding through an open transition sate and

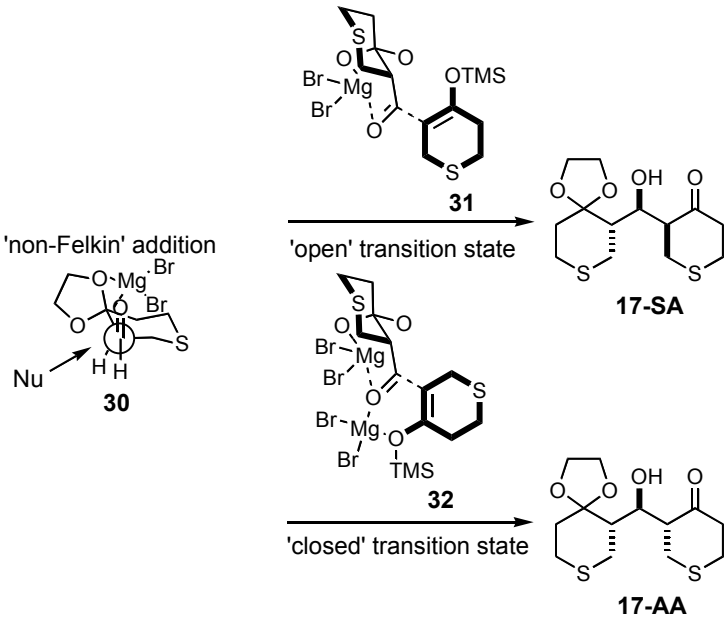
Felkin addition to chiral aldehyde **15** (Scheme 7). $MgBr_2{\cdot}OEt_2$ is used to generate the non-Felkin first aldol adducts **17-SA** and **17-AA** in a 3:1 ratio. They are produced via non-Felkin addition to chiral aldehyde **15** through an open and closed transition state as seen in Scheme 8. Mukaiyama type aldol reactions of **26** and **15** mediated by $MgBr_2{\cdot}OEt_2$ are highly non-Felkin selective. This can be rationalized by assuming that the Mg^{2+} forms a complex (**31** and **32**) with simultaneous coordination to the carbonyl oxygen and the *cis* oxygen of the ketal group of **15** (Scheme 8).



Scheme 6. Mono-aldol formation and isomerization**.**



Scheme 7. Proposed nonchelation transition state for Felkin addition to **15**.

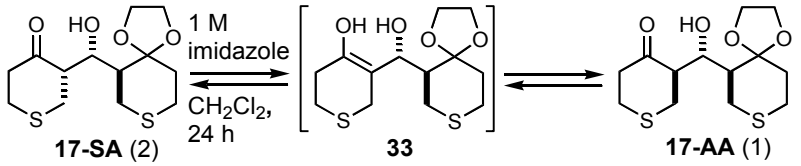


Scheme 8. Proposed chelation transition state for non-Felkin addition of **25** to **15**.

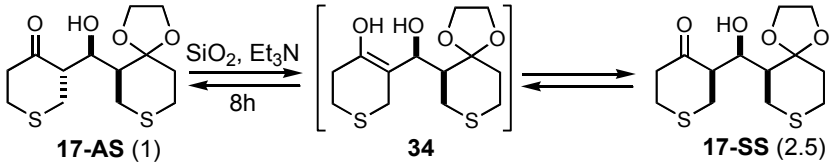
Synthetically useful syn-anti isomerization reactions of aldol adducts have been developed by the Ward group.[8] Syn-anti isomerization can occur by two distinct mechanisms: i) via retroaldol-aldol or ii) via keto-enol tautomerization. For adducts such as **17** with three

stereocenters, these mechanisms can be distinguished by examining the product distribution. If the isomerization occurs via a retroaldol-aldol process, isomerization would be expected to produce a mixture of all four possible diastereomers in a ratio reflecting their relative thermodynamic stability. However, if the reaction occurs via a keto-enol tautomerization, only 2 diastereomers are possible. Isomerization of each of the diastereomers of **17** revealed that the reaction occurs with little elimination and little retro-aldol. In each case, only the pair of diastereomers related by keto-enol tautomerism was present and other aldol isomers from retroaldol-aldol followed by a subsequent aldol reaction were not detected. Thus, it was concluded that the isomerization occurs via a keto-enol tautomerization.

This isomerization process has proven useful both as a tool for structure determination and as a viable method to obtain certain aldol diastereomers. For example, **17-AA** is the minor adduct obtained from the $MgBr_2 \cdot OEt_2$-mediated aldol reaction of **15** with **26**. However, this adduct can be obtained by isomerization of **17-SA**, the major adduct from that aldol reaction (Scheme 9). Similarly, the readily obtained enantiopure adduct **17-AS** can be efficiently isomerized to enantiopure **17-SS** (Scheme 10).



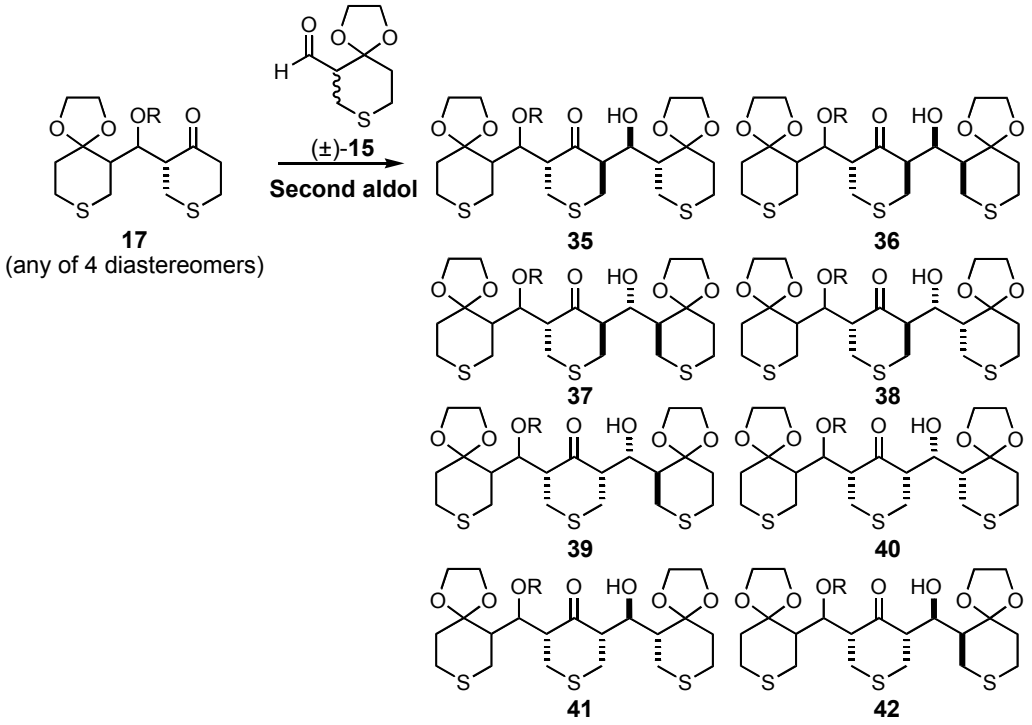
Scheme 9. Isomerization of non-Felkin first aldol products.[8]



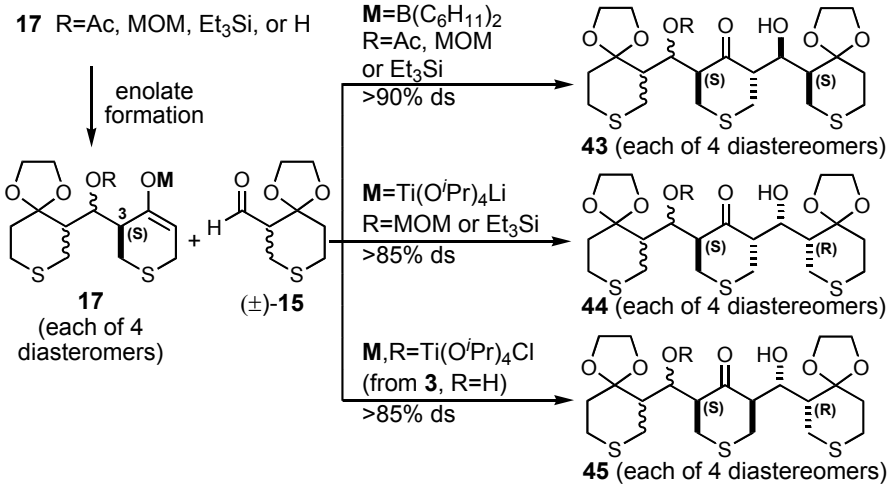
Scheme 10. Isomerization of Felkin first aldol products.[9]

The second aldol reaction of each of the four diastereomers of **17** with **15** has been explored. For each of the four possible diastereomers of **17**, an aldol reaction with racemic **15** can produce up to eight bis-aldol diastereomers **18** (Scheme 11). Nonetheless, these reactions

can be conducted with remarkable stereoselectivity. Depending on the reaction conditions and whether the OH group is protected or not, each of the diastereomers of **17** can produce any one of three diastereomers of **18** with high selectivity (Scheme 12). Accordingly, 11 of 20 possible diastereomers of **18** can be obtained selectively in only 6-7 steps from **19**.

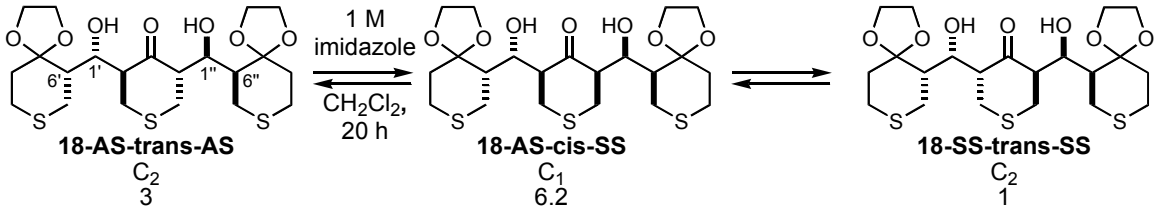


Scheme 11. Eight bis-aldol diastereomers possible from any diastereomer of **17**.

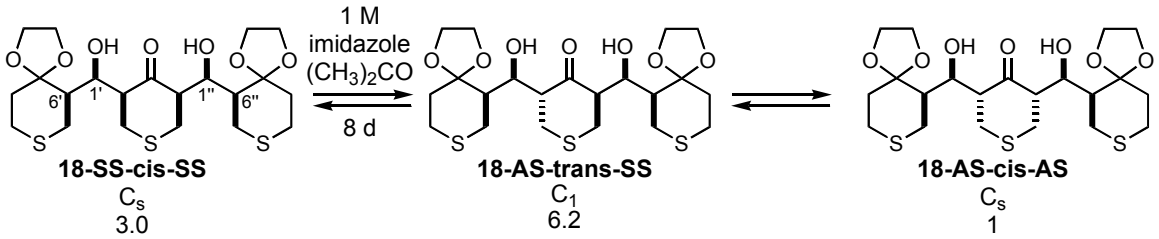


Scheme 12. Kinetic resolution to selectively give enantioenriched **43**, **44** and **45**.[10]

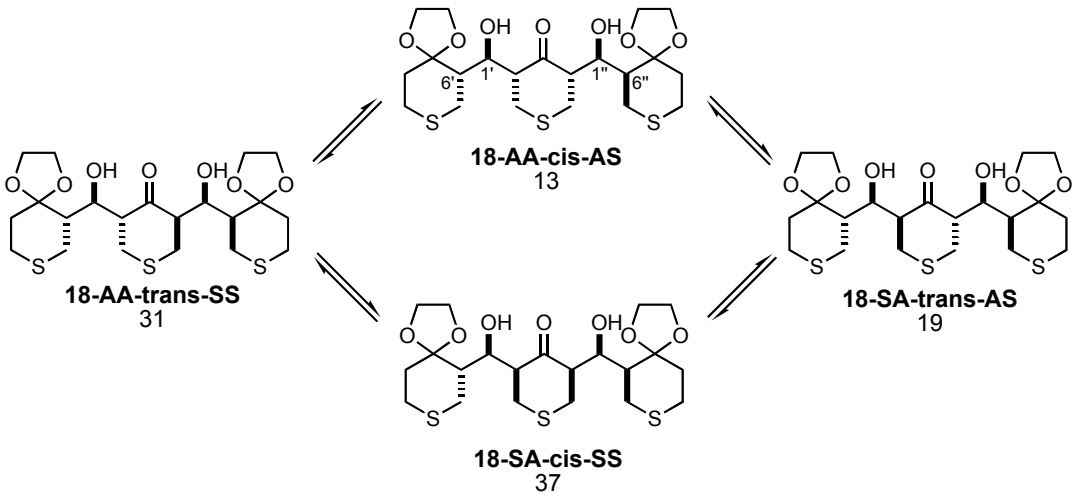
The generality of the isomerization process was extended to the bis-aldol diastereomers **18**. The bis-aldols **18** are able to isomerize at two sites, producing 3 or 4 diastereomers depending on the relative configuration at C-1' and C-6' compared to that at C-1'' and C-6''. When these relative configurations are the same (i.e., both syn or both anti), a set of three diastereomers are interrelated via isomerization by keto-enol tautomerism (Scheme 13 and Scheme 14). However, when these relative configurations are different (i.e. one syn and one anti), isomerization produces a set of four diastereomers (Scheme 15 and Scheme 16). Using the isomerization protocol, three new diastereomers of **18** were isolated: **18-SS-cis-SS** (Scheme 14), **18-SA-cis-SS** (Scheme 15) and **18-AA-cis-SS** (Scheme 16).



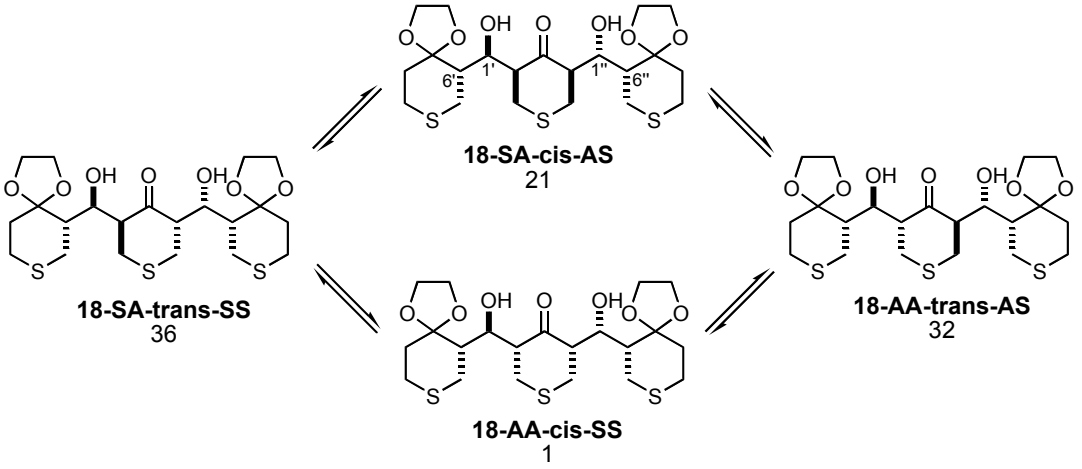
Scheme 13. Imidazole catalyzed isomerization to produce **18-AS-trans-AS**:**18-AS-cis-SS**:**18-SS-trans-SS** (3:6.2:1).[8]



Scheme 14. Imidazole catalyzed isomerization to produce **18-SS-cis-SS**:**18-AS-trans-SS**:**18-AS-cis-AS** (3.0:6.2:1).[8]



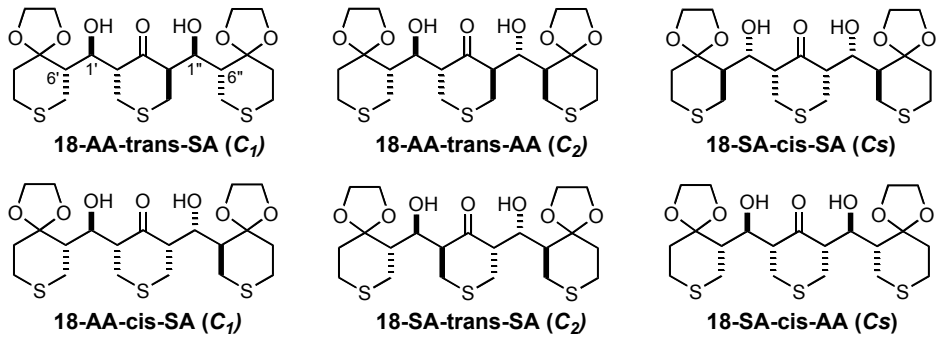
Scheme 15. Equilibrium in 0.8 M imidazole in CH_2Cl_2 after 20 hours at room temperature to produce **18-AA-trans-SS**:**18-AA-cis-AS**:**18-SA-trans-AS**:**18-SA-cis-SS** (31:13:19:37).[11]



Scheme 16. Equilibrium in 0.2 M imidazole in CH_2Cl_2 after 6 days at room temperature to produce **18-SA-trans-SS**:**18-SA-cis-AS**:**18-AA-trans-AS**:**18-AA-cis-SS** (36:21:32:1).[11]

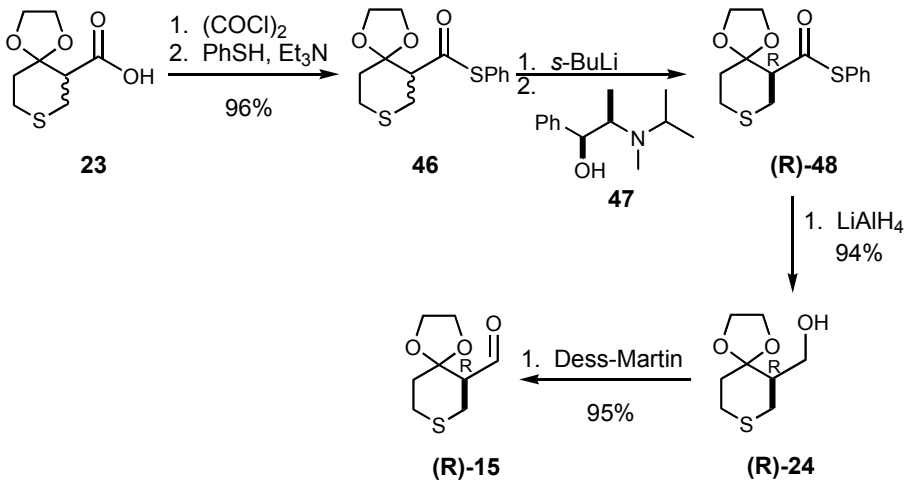
At the outset of this project, 14 of the 20 possible diastereomers of **18** had been synthesized; 11 of these are available stereoselectively and 3 by isomerization. The remaining six diastereomers all have the common feature of 1', 6' anti and 1", 6" anti relative topicity, arising from non-Felkin[1] addition to aldehyde **15** (Scheme 17).

[1] Non-Felkin refers to adducts resulting from addition of the non-Felkin face of aldehyde **15** resulting in adducts with (1'R*, 6"S*) relative configuration.

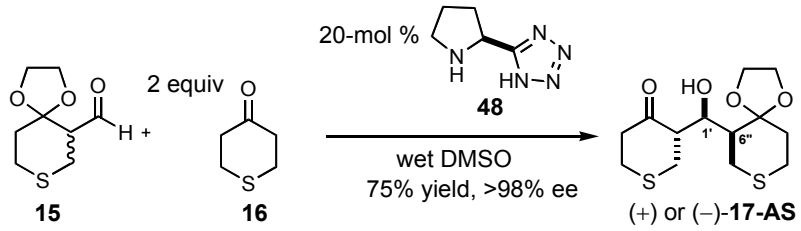


Scheme 17. The six hitherto unsynthesized bis-aldol diastereomers of the TR2P.

In nature, chiral polypropionates are usually found in enantiopure form. Using the TR2P, enantiopure adducts can be made via two methods. One option involves synthesizing enantiopure aldehyde (Scheme 5); however, the synthesis is difficult to scale up.[12] A second alternative is to employ an chiral mediator to generate enantioenriched aldol adducts from racemic aldehyde. This latter strategy is shorter and more efficient than synthesizing enantiopure aldehyde. By using the organocatalyst (S)-5-(pyrrolidin-2-yl)tetrazole **48**, the synthesis of enantiopure (-)-**17-AS** (>98% ee) can be performed on large scale with high yield (Scheme 19).[9] Enantiopure **17-SS** is easily made from **17-AS** via isomerization as previously discussed (Scheme 10).[8] Thus, both aldol adducts **17-AS** and **17-SS** derived from Felkin addition of **16** to **15** can be obtained in enantiopure form in 5 and 6 steps respectively from dimethyl 3,3'-thiobispropanoate **19**. The current method to synthesize the non-Felkin aldol adducts **17-AA** and **17-SA** requires the enantiopure aldehyde **15**.



Scheme 18. Synthesis of enantioenriched **(R)-1** by enantioselective deprotonation.[12]



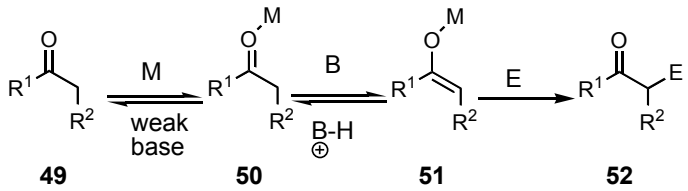
Scheme 19. Synthesis of non-racemic **17-AS**.[9]

1.2. Soft-enolization methodology

Using a weak base in combination with a Lewis acid to generate an enolate has been referred to as soft enolization. As will be discussed in the results and discussion, the soft enolization methodology was applied to the TR2P for the formation of mono-aldol adducts **17** and bis-aldol adducts **18**. A review of the literature on this methodology is presented below.

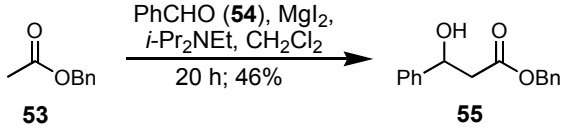
Enolates made via a weak base and Lewis acid are formed under mild conditions without having to work at low temperatures and under vigorous exclusion of air and moisture. The Lewis acid coordinates to the carbonyl oxygen and thereby increases the acidity of the α-proton so that a weak base is able to deprotonate it reversibly (Scheme 20). This soft enolization methodology has been applied towards different types of reactions including aldol reactions of thioesters, four component cascade aldol reactions, a Morita-Baylis-Hilman

reaction equivalent, Mannich addition, direct crossed Claisen coupling of thioesters and towards the synthesis of β-diketones.[13, 18]



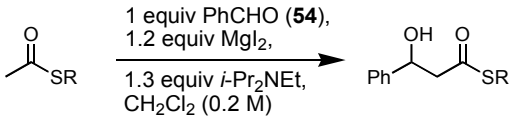
Scheme 20. Enolate formation via a weak base and Lewis acid.

Coltart has used soft enolization for aldol reactions of simple thioesters.[13, 14] Of the metal salts examined including zinc(II) chloride, copper(II) acetate, and nickel(II) bromide, only magnesium iodide and magnesium bromide could mediate the reaction between benzyl acetate (**53**) and benzaldehyde (**54**) (Scheme 21).[13] The scope of the reaction was expanded by using thioesters (Table 1).[13]



Scheme 21. MgI_2 mediated aldol reaction between benzyl acetate (**53**) and benzaldehyde (**54**).

Table 1. Screening of thioesters **55**-**60** in the MgI_2 mediated aldol reaction with benzaldehyde **54**

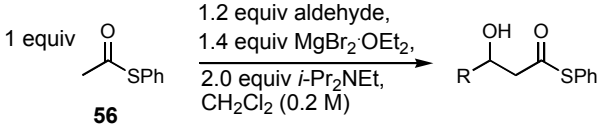


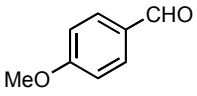
Entry	Thioester R =	Time (min)	Isolated yield (%)
1	Bn (**55**)	25	95
2	Ph (**56**)	20	94
3	*p*-OMe-Ph (**57**)	20	98

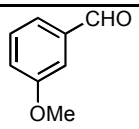
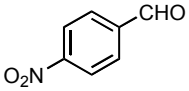
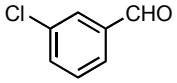
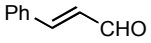
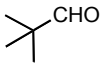
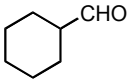
4	*o*-OMe-Ph (**58**)	20	96
5	*p*-NO_2-Ph (**59**)	60	92
6	-CH_2-furan (**60**)	30	96

The cheaper $MgBr_2 \cdot OEt_2$ could easily be substituted for MgI_2. No increase in yield or decrease in reaction time was observed when anhydrous CH_2Cl_2 was used, nor when the reaction was performed with the strict exclusion of air and moisture under an argon atmosphere. Other solvents were tried including tetrahydrofuran, diethyl ether, N,N-dimethylformamide, ethyl acetate, benzene, and toluene but lead to no improvement in yield. Bases explored include triethylamine, pyridine, 5-methoxybenzimidazole, 2,6-lutidine, 1,8-diazabicyclo[5.4.0]undec-7-ene, 1,5-diazabicyclo[4.3.0]non-5-ene, and 2-tert-butyl-1,1,3,3-tetramethylguanidine. However, N-diisopropyl-N-ethylamine (*i*-Pr_2NEt) was found to be the superior base. Substituted aromatic and aliphatic aldehydes could also perform the direct aldol addition with thioesters in high yield and low reaction times (Table 2).

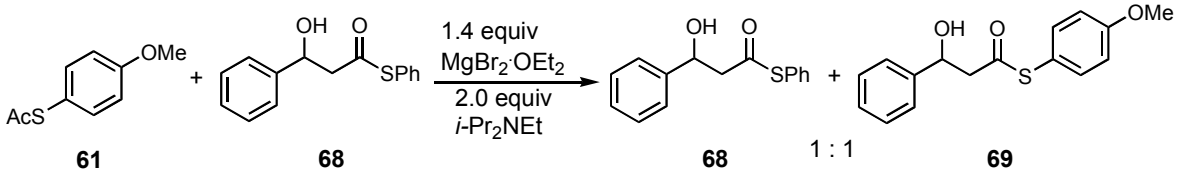
Table 2. Screening of aldehydes **61**-**67** in the $MgBr_2 \cdot OEt_2$ mediated aldol reaction with S-phenyl thioacetate **56**



Entry	Aldehyde	Time (min)	Isolated yield (%)
1	PhCHO (**54**)	30	96
2	 **61**	30	97

3	 **62**	30	96
4	 **63**	60	94
5	 **64**	60	95
6	 **65**	60	92
7	 **66**	60	94
8	 **67**	60	82

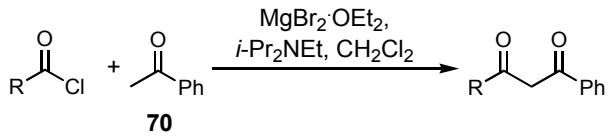
The reversibility of the reaction was explored by combining β-hydroxythioester, N,N-diisopropylamine, and a competing thioester. This experiment resulted in a 1:1 mixture of both β-hydroxythioster products, suggesting that the aldol addition is reversible under the reaction conditions (Scheme 22).[13]



Scheme 22. $MgBr_2 \cdot OEt_2$ mediated reaction between **61** and **68** to determine the reversibility of the reaction.

The soft enolization methodology can be applied to the formation of 1,3-diketones. Reaction of acetophenone (**70**) with benzoyl chloride (**71**) in the presence of $MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt generated the β-diketone in good yield after 1 hour (Table 3).[15] 3,3-Dimethylbutanoyl chloride (**72**) similarly generated the corresponding 1,3-diketone, albeit in lower yield. When pentanoyl chloride (**73**) was used, the 1,3-diketone was produced in low yield (30%) along with formation of the bis-acylated product (Table 3).[15]

Table 3. Screening of benzoyl chlorides **71**-**73** on β-diketone formation

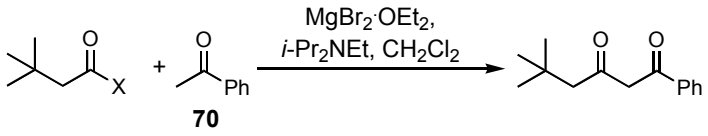


70

Entry	R	Isolated yield (%)
1	Ph (**71**)	83
2	CH_2*t*-Bu (**72**)	65
3	Bu (**73**)	30

A study of the acylating agent revealed that ameliorated yields and reaction times were obtained with pentaflurophenyl ester (**76**) and N-acylbenzotriazoles (**77**) resulting in greater than 90% yields with short reaction times (Table 4).[15] These acylating agents are less sensitive to water than the acid chlorides, so the reaction could be performed open to the air in untreated, reagent grade CH_2Cl_2 with no change in yield. The nucleophilic acylation catalyst DMAP did not improve the reaction in terms of time or yield (Table 4).[15]

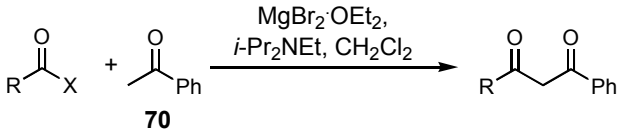
Table 4. Screening of acylating agents **72**-**77** on β-diketone formation with acetophenone **70**

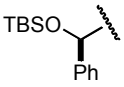
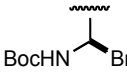


Entry	Acylating agent X	Nucleophilic acylation catalyst	Time (h)	Isolated yield (%)
1	Cl (**72**)		1	63
2	Cl (**72**)	DMAP	1	65
3	O-succinimide (**74**)			NR
4	SC_6H_4-4-NO_2 (**75**)		24	40
5	SC_6H_4-4-NO_2 (**75**)	DMAP	24	39
6	OC_6F_5 (**76**)		12	79
7	OC_6F_5 (**76**)	DMAP	12	80
8	OC_6F_5 (**76**)		24	92
9	benzotriazole (**77**)		3	96
10	benzotriazole (**77**)	DMAP	3	92

Differently substituted pentafluorophenyl esters and N-acylbenzotraizoles acylating agents could be employed to generate the corresponding 1,3-diketone. N-Acylbenzotriazoles performed better than the pentafluorophenyl esters in most cases, resulting in high yields and low reaction times (Table 5). This study also demonstrated that the reaction conditions did not induce epimerization of a stereocentre α to a carbonyl (Table 5, Entries 7 and 8).[15]

Table 5. Effect of acylating agent on formation of β-diketone with acetophenone **70**

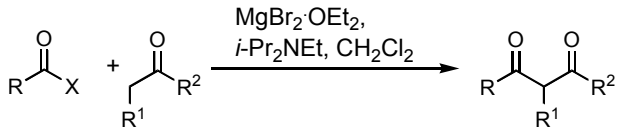


Entry	X	R	1,3-diketone	Time (h)	Isolated yield (%)
1	Bt	CH_2*t*-Bu (**77**)		2.5	96
2	O-Pfp	CH_2*t*-Bu (**76**)		24	92
3	Bt	*t*-Bu (**78**)		4	99
4	O-Pfp	*t*-Bu (**79**)		24	81
5	Bt	Ph (**80**)		2.5	95
6	O-Pfp	Ph (**81**)		24	87
7	Bt	 (**82**)		4	91
8	O-Pfp			24	86
9	Bt	Bu (**83**)		2.5	79
10	O-Pfp	Bu (**84**)		24	61
11	O-Pfp	 (**85**)		24	73
12	Bt	$CH_2CH_2CHCH_2$ (**86**)		3	70
13	O-Pfp	$CH_2CH_2CHCH_2$ (**87**)		24	53
14	Bt	(E)-CHCHPh (**88**)		2.5	81

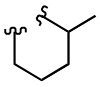
Coltart explored the scope of the reaction with respect to the ketone. All reported ketones generated the corresponding product in yields of 50% or greater. Interesting, 1-[(*E*)]-cinnamoyl]-1*H*-benzotriazole **88** and 3-pentanone **97** coupled without further cyclization to the

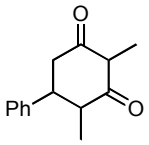
1,3-cyclohexanedione **98** (Table 6, entry 18 and Figure 1).[15] Other Lewis acids explored include $ZnCl_2$, $CuOTf_2$, and NiI_2 with solvents CH_2Cl_2, THF, and toluene but no improvement in the reaction was found (Table 7).[16]

Table 6. Reaction scope on the $MgBr_2 \cdot OEt_2$ promoted formation of β-diketones



Entry	R	X	R^1	R^2	Time (h)	Isolated yield (%)
1	CH_2t-Bu	Bt (**77**)	H	2-OMe-C_6H_4 (**89**)	2.5	92
2	CH_2t-Bu	O-Pfp (**76**)	H	2-OMe-C_6H_4 (**89**)	24	68
3	CH_2t-Bu	Bt (**77**)	H	4-OMe-C_6H_4 (**90**)	4	99
4	CH_2t-Bu	O-Pfp (**76**)	H	4-OMe-C_6H_4 (**90**)	24	99
5	CH_2t-Bu	Bt (**77**)	H	2-furanyl (**91**)	2.5	91
6	CH_2t-Bu	O-Pfp (**76**)	H	2-furanyl (**91**)	24	72
7	CH_2t-Bu	Bt (**77**)	Me	Ph (**92**)	4	92
8	CH_2t-Bu	O-Pfp (**76**)	Me	Ph (**92**)	24	65
9	CH_2t-Bu	Bt (**77**)	OTBS	Ph (**93**)	2.5	65
10	CH_2t-Bu	O-Pfp (**76**)	OTBS	Ph (**93**)	24	68
11	CH_2t-Bu	Bt (**77**)	H	2-OH-C_6H_4 (**94**)	24	50
12	CH_2t-Bu	O-Pfp (**76**)	H	2-OH-C_6H_4 (**94**)	24	65

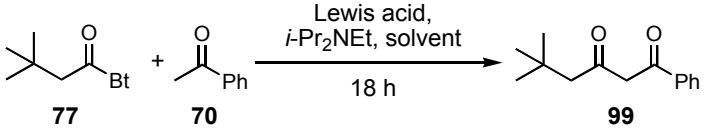
13	CH_2*t*-Bu	Bt (**77**)	 (**95**)		3	99
14	CH_2*t*-Bu	O-Pfp (**76**)			24	58
15	CH_2*t*-Bu	Bt (**77**)	 (**95**)		3	66
16	CH_2*t*-Bu	O-Pfp (**76**)			24	62
17	Ph	Bt (**80**)	Me	(E)-CHCHPH (**96**)	3	81
18	(E)-CHCHPh	Bt (**88**)	Me	Et (**97**)	16	72



98

Figure 1. Undetected cyclized 1,3-cyclohexanedione **98** from the coupling of 1-[(*E*)]-cinnamoyl]-1*H*-benzotriazole **88** and 3-pentanone **97**

Table 7. Screening of Lewis acid on β-diketone formation

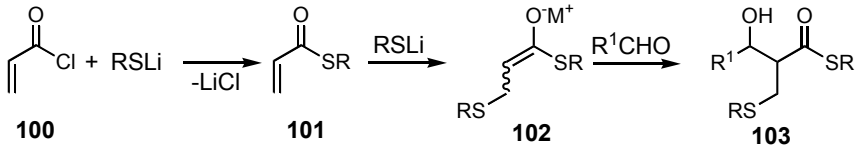


77 **70** **99**

Entry	Lewis acid	Solvent	Conversion (%)
1	$MgBr_2 \cdot OEt_2$	CH_2Cl_2	96
2	$MgBr_2 \cdot OEt_2$	THF	94
3	$MgBr_2 \cdot OEt_2$	toluene	82
4	$ZnCl_2$	CH_2Cl_2	61
5	$ZnCl_2$	THF	trace
6	$ZnCl_2$	toluene	9
7	$Cu(OTf)_2$	CH_2Cl_2	trace

8	$Cu(OTf)_2$	THF	trace
9	$Cu(OTf)_2$	toluene	trace
10	NiI_2	CH_2Cl_2	NR
11	NiI_2	THF	NR
12	NiI_2	toluene	NR

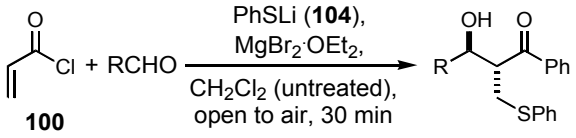
Coltart and co-workers have studied a four-component cascade aldol addition of thioester enolates with enolizable aldehydes (Scheme 23).[17] In one pot, an anti-selective aldol addition from 2 equivalents of a thiolate, one equivalent of an α,β-unsaturated acid chloride and one equivalent of an aldehyde is possible. The reaction proceeds via acyl transfer of the thiolate onto the α,β -unsaturated acid chloride (Scheme 23). The second equivalent of thiolate can add via 1,4-addition to the α,β-unsaturated thioester. This process generates a thioester enolate which can undergo an aldol reaction with an aldehyde (**Error! Reference source not found.**).



Scheme 23. Four component cascade reaction: formation of thioester enolate followed by aldol addition to the aldehyde.

The four component aldol addition was attempted with $MgBr_2 \cdot OEt_2$, PhSLi (**104**) and acryloyl chloride (**100**) (Table 8). Within 30 minutes, the reaction had reached completion and gave the desired product in 67% yield with a high anti: syn ratio of 13:1 in favour of the anti diastereomer. The yield could be improved to 88% by employing 1.2 equivalents of $MgBr_2 \cdot OEt_2$, 3 equivalents of PhSLi (**104**), and 1.5 equivalents of acryloyl chloride (**100**). No aldol product was observed in the absence of $MgBr_2 \cdot OEt_2$. Other aldehyde acceptors were investigated and all generated the aldol addition products in high yields and high diastereoselectivity in favour of the anti diastereomer (Table 8).[17]

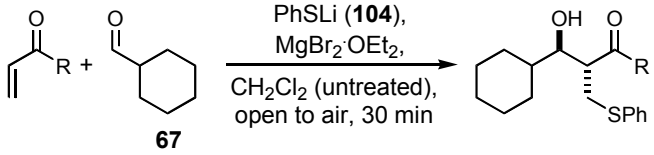
Table 8. Screening of aldehydes **54**, **67**, **105-108** in the $MgBr_2 \cdot OEt_2$ mediated four component aldol addition with acryloyl chloride **100**



Entry	R=	Yield (%)	*Anti*:*Syn* Diastereoselectivity
1	-Ph (**54**)	88	13:1
2	$-(CH_2)_2CH_3$ (**105**)	71	11:1
3	$-(CH_2)_6CH_3$ (**106**)	68	16:1
4	$-(CH_2)_2Ph$ (**107**)	71	14:1
5	$-C_6H_{11}$ (**67**)	81	>20:1
6	$-CH(CH_3)_2$ (**108**)	76	>20:1

The scope of the reaction could be expanded to include other acrylate reagents. Oxoesters as well as N-phenyl amide showed low diastereoselectivity in favour of the anti diastereomer. In addition, the other thioesters investigated showed diminished diastereoselectivity to as low as 1.5:1 (S-*tert*-butyl thioester (**110**), Entry 4, Table 9).[17]

Table 9. Screening of acrylate reagents **109-115** in the $MgBr_2 \cdot OEt_2$-mediated four component aldol addition with cyclohexanal **67**

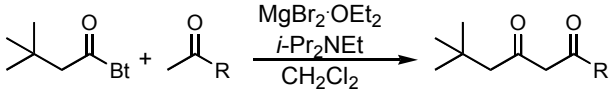


Entry	R=	Yield (%)	anti-syn Diastereoselectivity
1	-SPh (**109**)	79	>20:1

2	-SC_6H_3-2,6-Me (**110**)	60	11:1
3	-SEt (**111**)	82	4:1
4	-S*t*-Bu (**112**)	77	1.5:1
5	-OPh (**113**)	72	2:1
6	-O*t*-Bu (**114**)	78	1:1
7	-NHPh (**115**)	64	2:1

The soft enolization methodology was applied to a direct crossed-Claisen coupling of thioesters by Coltart et al. When N-acylbenzotriazole and thioesters were reacted under soft enolization conditions ($MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt), the desired β-diketones were isolated in high yields (Table 10).[18] Both reagents have an α-proton able to undergo deprotonation to form the enolate anion. However, no self-addition products or the other crossed-Claisen products were detected. Oxoesters did not perform as well as thioesters (entry 1 versus entry 2) and aliphatic thioesters were lower yielding than aromatic thioesters.[18]

Table 10. $MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt promoted Crossed-Claisen with benzotriazole **54** and thio/oxo-esters

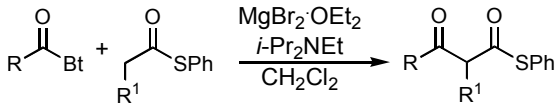


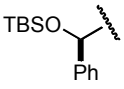
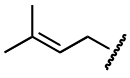
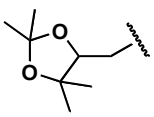
77

Entry	R=	Time (h)	Yield (%)
1	-SPh (**32**)	4	93
2	-OPh (**139**)	26	44
3	-SEt (**140**)	4	83
4	-SBn (**55**)	4	80

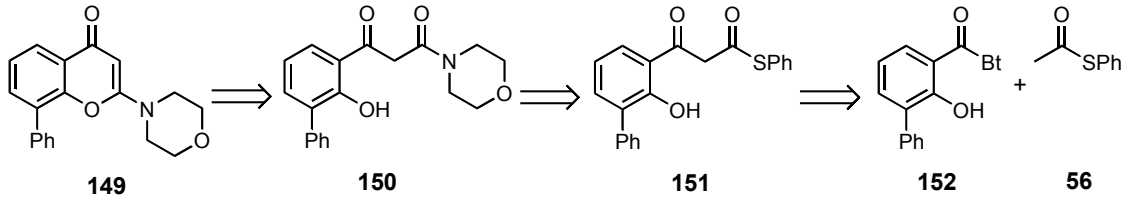
The scope of the crossed-Claisen coupling via soft enolization was explored by varying the thioester component and the N-acylbenzotriazole component (Table 11). The reaction could be performed on reactants with varying functional groups including ester, acetal, alkenes and α,β-unsaturated carbonyl compounds. The β-keto-thioesters produced from these reactions can directly be made into β-keto thioesters, amides and β-diketones.[18]

Table 11. Scope of $MgBr_2 \cdot OEt_2$ and i-Pr_2EtN mediated crossed-Claisen reaction



Entry	R	R^1	Yield (%)
1	-CH_2*t*-Bu (**77**)	-Me (**134**)	87
2	-CH_2*t*-Bu (**77**)	-$CH_2CH_2CH_3$ (**141**)	85
3	-CH_2*t*-Bu (**77**)	-CH_2Ph (**142**)	88
4	-CH_2*t*-Bu (**77**)	-OBn (**143**)	78
5	-Ph (**80**)	-Me (**134**)	91
6	-*i*-Pr (**144**)	-Me (**134**)	91
7	-(E)-CHCHPh (**88**)	-Me (**134**)	76
8	-C_6H_{11} (**145**)	-Me (**134**)	90
9	 (**82**)	-Me (**134**)	64
10	-*o*-(CO_2Me)-Ph (**146**)	-Me (**134**)	87
11	-*o*-(CO_2Me)-Ph (**146**)	 (**147**)	92
12	-*o*-(CO_2Me)-Ph (**146**)	 (**148**)	80

The crossed Claisen coupling with $MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt was applied to the total synthesis of LY294002 (**149**). It is a potent, specific inhibitor of PI3-K which is involved in many diseases including diabetes, cancer, and chronic inflammation.[18] The key step in the synthesis was a direct crossed-Claisen coupling to demonstrate the utility of the soft enolization methodology (Scheme 24).[18] This methodology accessed LY294002 (**149**) in 7 steps and 67% overall yield, thus demonstrating the usefulness of the direct crossed-Claisen coupling with $MgBr_2 \cdot OEt_2$ and *i*-Pr_2NEt.



Scheme 24. $MgBr_2 \cdot OEt_2$ promoted direct crossed-Claisen coupling towards the synthesis of LY294002 (**149**).

The scope of the soft enolization methodology has been expanded from aldol additions with thioesters to cascade reactions, Mannich additions and Claisen condensations for simple systems by Coltart. Herein, we have applied the soft enolization methodology to the TR2P. The Results and Discussion chapter will discuss the highly diastereoselective direct aldol reactions of thiopyran substrates (**16** and **17** with **15**) via soft enolization.

1.3. Research Objective

The current synthetic route for the preparation of enantiopure non-Felkin tetrapropionate synthons is a limitation of the TR2P. Enantiopure tetrapropionate synthons **17-AS** and **17-SS** resulting from Felkin addition of **16** to **15** are directly accessible using the organocatalyst (S)-5-(pyrrolidin-2-yl)tetrazole **48**. However, non-racemic first aldol adducts **17-AA** and **17-SA** from non-Felkin addition are made via enantiopure aldehyde **15**. A more direct approach to enantioenriched **17-AA** and **17-SA** is required. The goal of the this research was to develop a methodology using chiral transition metal-based Lewis acids and/or chiral

organocatalysts with chelating Lewis acids to access non-racemic non-Felkin first aldol adducts. This methodology could then be extended to access new hexapropionate synthons by non-Felkin addition of **17-AA** or **17-SA** to **15**.

2. RESULTS AND DISCUSSION

2.1. Transition metal catalysis – Bis(oxazoline) ligands

Chiral C_2-symmetric bis(oxazoline) (BOX) ligands are an important ligand class for asymmetric catalysis.[19-25] They are used to prepare catalysts for various enantioselective reactions, including inter- and intramolecular cyclopropanations, aziridinations, Michael additions, Mukaiyama-Michael reactions, allylic substitution reactions, radical reactions, Diels-Alder reactions, hetero Diels-Alder reactions, 1,3-dipolar cycloaddition reactions, ene and hetero ene reactions, as well as Mukaiyama aldol reactions.[20] BOX ligands have been successfully used for many applications due to the readily tuneable nature of the ligand structure (Figure 2). The R groups, counter-anion and metal centre are all easily adjustable. BOX ligands are a good choice for enantioselective catalysis due to the rigidity of the ligand and the resulting close proximity of the two substituents to the coordination site of the metal centre.[21]

BOX ligands are attractive due to their easy synthesis from readily available amino alcohols. Synthesis of the C_2-ligand **154** is a one step procedure starting from the amino alcohol (Figure 2).[22] The catalyst can be prepared by reacting the ligand with an equimolar quantity of a metal salt. The choice of R group, counter-anion, and metal can be altered to modify the rate and selectivity of a particular reaction.

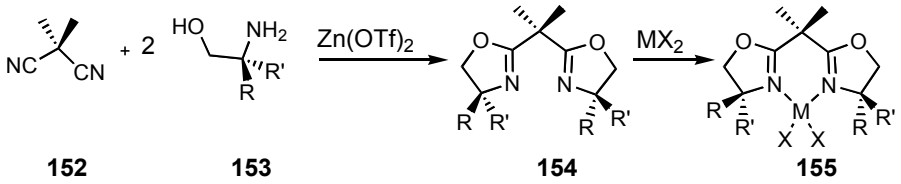


Figure 2. Synthesis of BOX metal complex from 2,2-dimethylmalononitrile **152** and β-amino alcohol **153**.

Non-symmetric BOX ligands can be synthesized in a similar manner, constructing one oxazoline ring at a time (Figure 3). The first oxazoline ring is formed using $Zn(OAc)_2$ as catalyst

and the second oxazoline ring is formed in a subsequent step using $Zn(OTf)_2$.[23] The resulting BOX-metal complex contains sterically different but electronically equivalent coordination points for the incoming reactant to coordinate to. Thus, the selectivity of the reaction can be further manipulated.

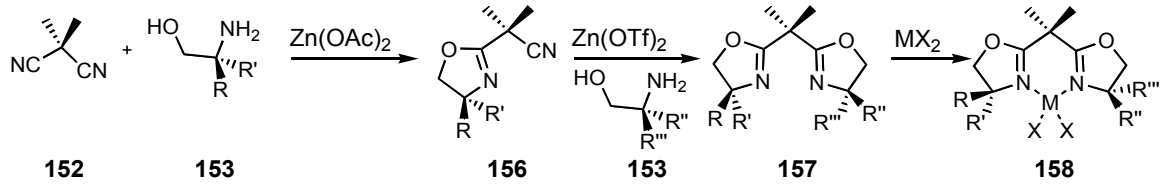


Figure 3. Synthesis of non-symmetric bis(oxazoline) complex **158** from 2,2-dimethylmalonylnitrile **152** and two different β-amino alcohols **153**.

The Lewis acidity of the BOX-metal complex can be tuned by varying the counter ion. For example the triflate (-OTf) is weakly bound to the metal centre while hexafluoroantimonate (SbF_6-) counter ions are fully dissociated from the metal centre. Thus, the SbF_6-counter ions make the complex more Lewis acidic than the -OTf counterpart. Complexes with SbF_6-counterions are made via anion exchange from the corresponding chlorides by treatment with 2 equivalents of $AgSbF_6$ and removal of the AgCl by-product through filtration (Figure 4).

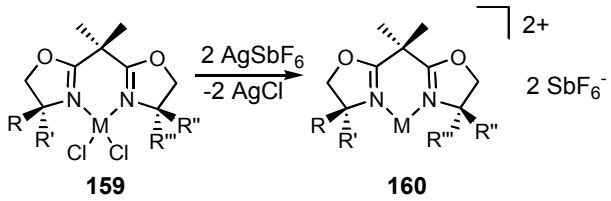
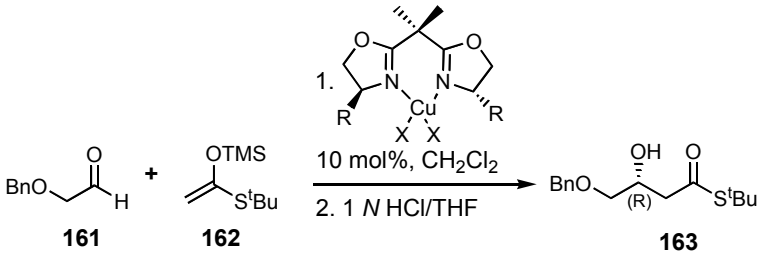


Figure 4. Formation of SbF_6-BOX complex from the corresponding chloride salt.

Copper(II) bis(oxazoline) (BOX) catalysts **155** (Figure 2) and copper(II) bis(oxazolinyl)pyridine (PYBOX) catalysts are active Lewis acid catalysts first reported in 1991 by Evans[24] and Corey.[25] Evans and coworkers have shown that these chiral Lewis acids are effective catalysts for the Mukaiyama aldol reaction with aldehyde substrates that are capable of chelation. Evans and coworkers reported a catalytic enantioselective aldol addition of enolsilanes to (benzyloxy)acetaldehyde catalyzed by C_2-symmetric copper(II) BOX and PYBOX

complexes.[19] Bis(oxazoline) and bis(oxazolinyl)pyridine ligands were screened for the aldol addition of **162** to (benzyloxy)acetaldehyde **161** (Table 12 and Table 13). Complex **173** was found to be the optimal catalyst and was the catalyst chosen to explore other reaction parameters.

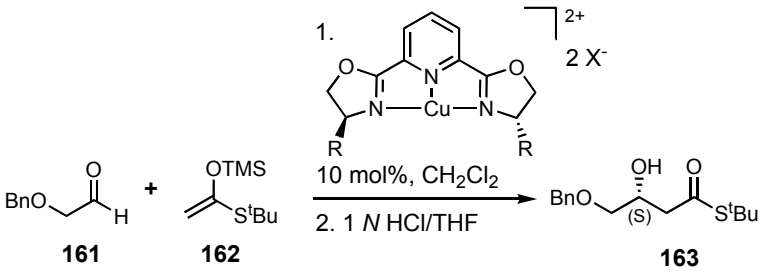
Table 12. Screening of BOX catalysts **164**-**168** in the Mukaiyama aldol reaction of **161** with **162**



Entry	R	X	Time (-78 °C)	ee (%) [a]
1	Ph	OTf (**164**)	15 min	9 (R)
2	$CHMe_2$	OTf (**165**)	15 min	9 (S)
3	Bn	OTf (**166**)	60 min	88 (R)
4	CMe_3	OTf (**167**)	60 min	91 (R)
5	CMe_3	SbF_6 (**168**)	15 min	≤64 (S)

[a] Enantiomeric excess determined by HPLC using a Chiralcel OD-H column. Absolute configuration determined by comparison of the optical rotation to literature values.

Table 13. Screening of PYBOX catalysts **169**-**173** in the Mukaiyama aldol reaction of **161** with 162



Entry	R	X	Time (T °C)	ee (%) [a]

1	CMe_3	SbF_6 (**169**)	12 h (-78)	62
2	$CHMe_2$	SbF_6 (**170**)	15 min (-78)	85
3	Bn	SbF_6 (**171**)	15 min (-78)	67
4	Ph	OTf (**172**)	60 min (-78)	96
5	Ph	SbF_6 (**173**)	15 min (-78)	99
6	Ph	SbF_6 (**173**)	-50 [b]	87
7	Ph	SbF_6 (**173**)	-20 [b]	82
8	Ph	SbF_6 (**173**)	0 [b]	78

[a] Enantiomeric excess determined by HPLC using a Chiralcel OD-H column. Absolute configuration determined by comparison of the optical rotation to literature values. [b] Time for complete reaction was not determined in temperature profile study.

Evans and coworkers examined the effect of aldehyde chelation. Complex **173** was found to catalyze the reaction of (benzyloxy)acetaldehyde **161** with silylketene acetal **162** to afford **163** in high enantioselectivity. However, the same catalyst yields a less enantioselective process with an aldehyde that is a weaker chelator. For example, aldehyde **174** yielded a product with significantly reduced ee (Entry 2, Table 14). Further, catalyst **173** yields nearly racemic product when an aldehyde totally incapable of chelation (**175**) is used (Entry 2, Table 14).[19]

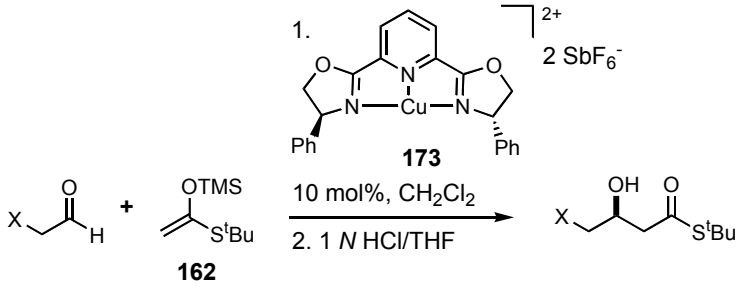


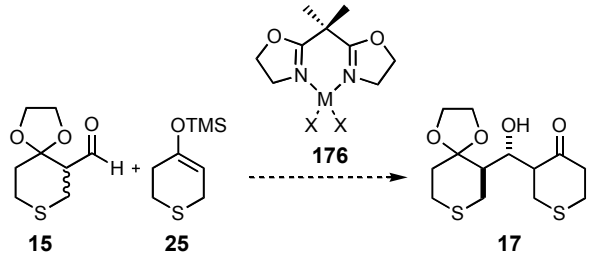
Table 14. Scope of aldehyde to determine requirement for aldehyde chelation

Entry	**X**	**ee (%)**
1	OBn (**161**)	99

2	OTBS (**174**)	56
3	CH_2Ph (**175**)	<10

In order to achieve good levels of enantioselectivity, the substrate must be able to chelate to the metal centre. Racemic products are obtained when substrates incapable of chelation are employed.[19] Aldehyde **15** is capable of chelation and further, chelating conditions favour high non-Felkin selectivity.[7] Thus, the use of Lewis acid catalysts incorporating BOX-type ligands to promote the aldol reaction of **25** with **15** might be suitable for the preparation of non-racemic C1'-C6'' anti (or non-Felkin) products.

Whether the BOX-complexes could catalyze an aldol reaction between **15** and **25** was investigated. Initially, achiral BOX complexes **176** were explored to determine whether the BOX chemistry could be applied to the TR2P. Unfortunately, BOX complexes prepared from copper(II) chloride or copper(II) triflate, were unable to catalyze any aldol reaction between **15** and **25**. Various Lewis acidic transition metal salts without additional ligands including copper chloride, copper triflate, magnesium triflate, magnesium perchlorate, zinc triflate, scandium triflate and hafnium triflate were also tested but none could catalyze the aldol reaction between **15** and **25**. This could arise because aldehyde **15** is less electrophilic than (benzyloxy)acetaldehyde **161** which bears an electronegative oxygen atom in the α-position. Additionally, silyl enol ether **25** is much less nucleophilic due to electronic (no sulfur) and steric reasons. Because adding a chelating ligand on the metal centre would reduce the Lewis acidity, further investigations into BOX systems were abandoned.



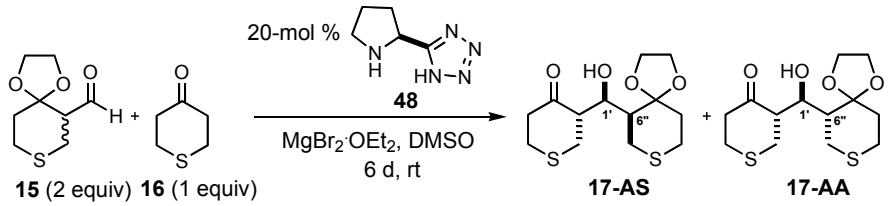
Scheme 25. Application of BOX chemistry to TR2P.

2.2. Organocatalysis – Modification of (S)-5-(pyrrolidin-2-yl)tetrazole catalyzed reaction

Drawing from prior work in the Ward group, reacting aldehyde **15** with ketone **16** in the presence of catalyst **48** produces **17-AS** in high yield (75%) and high enantiopurity (>98% ee) on multigram scale (Scheme 19).[9] A minor amount of **17-AA** is formed in the reaction (**17-AS**:**17-AA** ca 25:1) and its enantiomeric excess was determined to be 95%. Because the minor diastereomer was formed with such high enantiomeric excess, attempts were made to switch the diastereoselectivity of this reaction to favour **17-AA**. The hypothesis was that in the presence of a chelating Lewis acid the aldehyde diastereoface selectivity could be modulated, leading to the non-Felkin substrates.

When one equivalent of $MgBr_2 \cdot OEt_2$ was added, the enantiomeric excess of **17-AA** was >95% and the diastereomeric ratio was reduced from 25:1 to 12:1 of **17-AS** and **17-AA**, respectively (Table 15, Entry 1). Using excess aldehyde and three equivalents of $MgBr_2 \cdot OEt_2$ yielded approximately the same diastereomer ratio. However, using 6 equivalents of $MgBr_2 \cdot OEt_2$ further reduced the diastereomer ratio to 7:1 of **17-AS** and **17-AA**, respectively (Table 15, Entries 2 and 3).

Table 15. Effect of increasing equivalents of $MgBr_2 \cdot OEt_2$ on the (S)-5-(pyrrolidin-2-yl)tetrazole **48** catalyzed reaction of **15** and **16**.



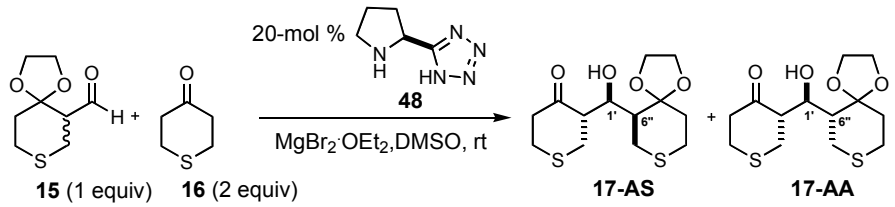
Entry	Equiv $MgBr_2 \cdot OEt_2$	Conc. (M)	Yield (%)	Diastereoselectivity
1 [a]	1	1.1	33	**17-AS** (12) : **17-AA** (1) [b]
2	3	0.4	24	**17-AS** (13) : **17-AA** (1)

3	6	0.2	31	**17-AS** (7) : **17-AA** (1)

[a] 1 equiv of **15;** reaction time 4 days. [b] **17-AA** was formed with >95% ee.

The effect of water as an additive was probed. Adding 1 equivalent of water to the reaction improved the ratio to 9:1 of **17-AS** and **17-AA**, respectively (Table 16, Entry 3).

Table 16. Effect of adding $MgBr_2 \cdot OEt_2$ to (S)-5-(pyrrolidin-2-yl)tetrazole (**48**) catalyzed reaction of **15** and **16**.

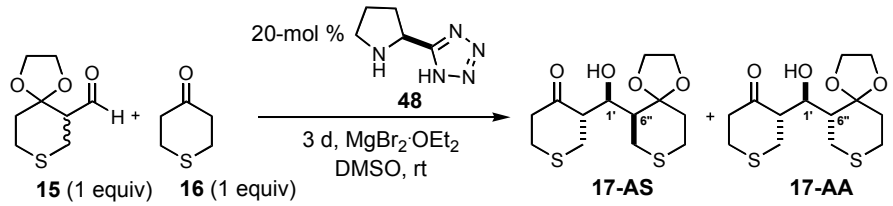


Entry	Equiv $MgBr_2 \cdot OEt_2$	Conc. (M) [c]	Time (d)	Yield (%)	Diastereoselectivity 17-AA : 17-SA : 17-AS : 17-SS	ee (%) [d]
1 [a, b]	0	9	8	75	1 : 0 : 25 : 0	>98 (**17-AS**), >95 (**17-AA**) [d]
2	3	0.4	6	40	1 : 0 : 13 : 0	
3 [b]	3	0.4	3	20 [e]	1 : 0 : 9 : 0	

[a] Literature result. [b] Equiv H_2O = 1.04. [c] With respect to aldehyde. [d] Determined by HPLC on a chiral stationary phase. [e] Conversion as determined by ^1H NMR.

The effects of concentration and stoichiometry of $MgBr_2 \cdot OEt_2$ were also examined. Lowering the concentration resulted in reduced yield and gave inferior diastereoselectivity (Table 17).

Table 17. Effect of concentration on adding $MgBr_2 \cdot OEt_2$ to the (S)-5-(pyrrolidin-2-yl)tetrazole (**48**) catalyzed aldol reaction of **15** and **16**.



Entry	Equiv $MgBr_2 \cdot OEt_2$	Conc. (M) [a]	Yield (%)	Diastereoselectivity 17-AA : 17-SA : 17-AS : 17-SS
1	1	0.9	44	1 : 0 : 11 : 0
2	2	0.6	40	1 : 0 : 14 : 0
3	3	0.5	28	1 : 0 : 16 : 0

[a] With respect to aldehyde **15**.

It is important to note that the (S)-5-(pyrrolidin-2-yl)tetrazole (**48**)-catalyzed reaction to produce enantioenriched **17-AS** is conducted at very high concentration and becomes a thick oil and eventually solidifies over the course of the reaction. The high concentration is necessary to keep reaction times reasonably low. At such high concentrations, effective mixing of $MgBr_2 \cdot OEt_2$ may be problematic. Stirring efficiency may have contributed to the variable yields and diastereoselectivities observed.

After further optimization efforts, the diastereoselectivity of the reaction of **15** with **16** catalyzed by **48** could not be improved to make the **17-AA** as the major adduct formed. Even in the presence of excess $MgBr_2 \cdot OEt_2$, the generation of **17-AS** is greatly favoured over **17-AA**. A dramatic reversal in the diastereoselectivity of the reaction with catalyst **48** would be required to make the reaction synthetically useful for the preparation of **17-AA**. Optimizing the reaction by altering concentration, stoichiometry, additives, etc was not deemed promising to produce synthetically useful amounts of **17-AA**.

2.3. Organocatalysis – *trans*-*N,N*-dialkylated diaminocyclohexane catalyst

As the combination of $MgBr_2 \cdot OEt_2$ in conjunction with **48** became less promising, alternative organocatalysts were considered. Luo and co-workers have reported the primary-tertiary-*trans*-diamine-Bronsted acid catalyst **179** for enantioselective aldol reactions of cyclic and acyclic ketones with aromatic aldehydes.[26] This novel organocatalyst exhibits high diastereoselectivity and enantioselectivity with a range of substrates, including the difficult aliphatic ketone substrates. A second acidic additive improved the catalysis, presumably by facilitating the enamine catalytic cycle. Remarkably, the primary-tertiary-*trans*-diamine catalyst **179** could provide syn selectivity with aliphatic ketones, a phenomenon not previously reported for organocatalysts. Cyclic ketones, only capable of forming *E*-enamines, produce anti aldol diastereoselectivity while the syn selectivity comes from the *Z*-enamines of the aliphatic ketones (Figure 5).

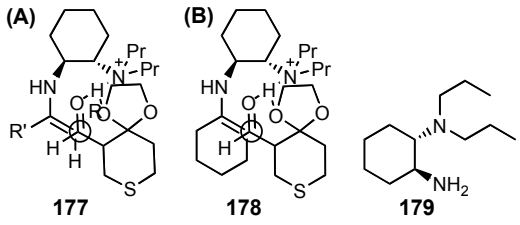


Figure 5. Proposed transition state for aldol reactions catalyzed by *trans*-N,N-dialkylated diaminocyclohexane catalyst **179** with (**A**) linear ketones **177** and (**B**) cyclic ketones **178**.

The primary-tertiary-*trans*-diamine catalyst **179** was appealing for the TR2P for several reasons. Primarily, it was hypothesized that the novel syn-enamine transition state proposed for this catalyst may produce non-Felkin adducts from **15** by simultaneous hydrogen bonding to the aldehyde carbonyl and the ketal. Secondly, the syn and anti aldol topicity could be exploited by using thiopyranone **16** to generate the anti adducts, while employing the linear ketone 5-pentanone **180** to generate syn adducts (Figure 6). The product **181** is viewed as a mono-desulfurized analogue of **17-SA**. In this way, the change in diastereoselectivity

characteristic of catalyst **179** for linear versus cyclic ketones might be exploited within the TR2P.

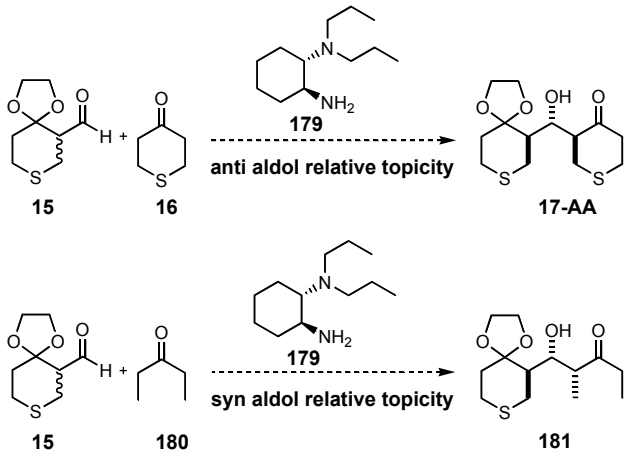
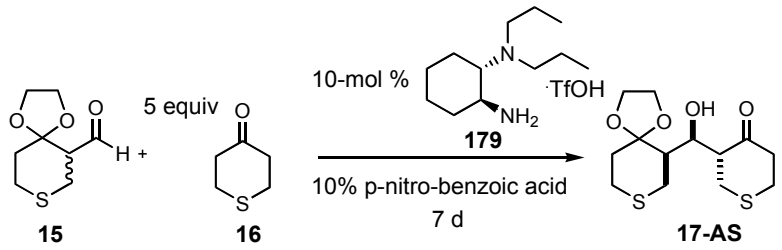


Figure 6. Proposed application of catalyst **179** to generate **17-AA** and the **17-SA** analogue **181**.

Catalyst **179** was prepared and applied to the aldol reaction of **15** with **16**. Under several conditions, the reaction was sluggish, producing low amounts of products. Employing the optimized conditions according to Luo,[26] 10% conversion to **17-AS** was observed after 7 days in all five solvents tested (Table 18). To increase the amount of non-Felkin products (**17-SA**, **17-AA**), the effect of adding $MgBr_2 \cdot OEt_2$ to this reaction was tested. When the amount of $MgBr_2 \cdot OEt_2$ was increased to three equivalents, 30% conversion to a mixture of three of the four aldol diastereomers could be detected (Table 19, entry 1). This result was promising as the non-Felkin/Felkin ratio[2] was 3:1. Varying the acid co-catalyst changed the diastereoselectivity while the conversion remained low (Table 19). Using 3 equivalents of $MgBr_2 \cdot OEt_2$, the reaction proceeded better with trifluoromethanesulfonic acid as co-catalyst and produced non-Felkin products exclusively. Unfortunately, under all conditions tested, the conversion and the enantioselectivity remained low.

[2] Ratio of (**17-AA**+**17-SA**):(**17-AS**+**17-SS**). Higher ratio indicates non-Felkin adducts predominate over Felkin adducts.

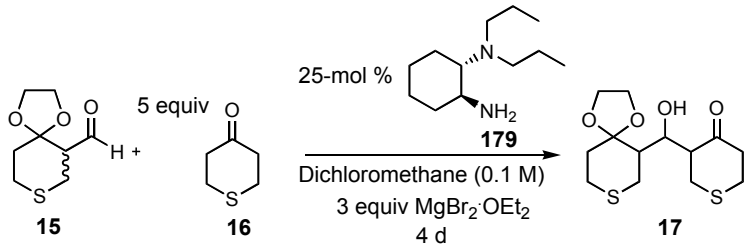
Table 18. Effect of solvent on the aldol reaction of **15** and **16** catalyzed by **179**



Entry	Solvent	Conversion (%) [a]
1	DMSO/H_2O	~10
2	DMSO	~10
3	CH_2Cl_2	~10
4	Toluene	~10
5	Methanol	~10

[a] Conversion from ^{1}H NMR.

Table 19. Effect of varying the co-catalyst on the aldol reaction between **15** and **16** catalyzed by **179**



Entry	Acid co-catalyst (equiv)	Conv (%) [a]	Diastereoselectivity [a] 17-AA : 17-SA : 17-AS : 17-SS	ee [b]
1 [c, d]	-	30	1 : 0.8 : 0.6 : 0	28% (**17-SA**)
2	TfOH (0.25)	20	1 : 0.8 : 0 : 0	11% (**17-SA**), 20% (**17-AA**)

3	TFA (0.25)	trace	-	
4	PTSA·H_2O (0.25)	~15	1 : 0.9 : 0 : 0	0% (**17-SA**)

[a] Determined by ^{1}H NMR of the crude reaction mixture. [b] Determined by chiral HPLC. [c] 10 equiv thiopyranone **16**. [d] 0.5 equiv catalyst **179**.

Although it was demonstrated that the diastereoselectivity of the first aldol reaction of the TR2P could be tuned in favour of non-Felkin products by addition of the chelating Lewis acid $MgBr_2{\cdot}OEt_2$, initial optimization attempts still resulted in low conversion and low enantiomeric excess. Varying the solvents from dichloromethane to toluene, methanol or dimethylsulfoxide resulted in low conversion to products. To account for the low enantiomeric excess and the low conversion it was hypothesized that the catalyst was simply acting as a base and deprotonating ketone **16** to form the magnesium enolate. To test this hypothesis, *N,N*-diisopropyl amine was chosen as the base due to its similarity to the tertiary amine portion of primary-tertiary *trans*-diamine catalyst **179**. Under similar conditions to those employed using **179**, 19% conversion (based on aldehyde) was obtained with three of the four diastereomers detected (Figure 7). This supports the notion that the tertiary-diamine portion of **179** was acting as a base to deprotonate the α-proton of **16**, suggesting that the magnesium enolate, not the enamine, was responsible for the conversion to products. The use of a weak base in combination with a Lewis acid had been explored by the Coltart group to mediate an aldol addition of thioesters and the results of this research was summarized in Chapter 1.

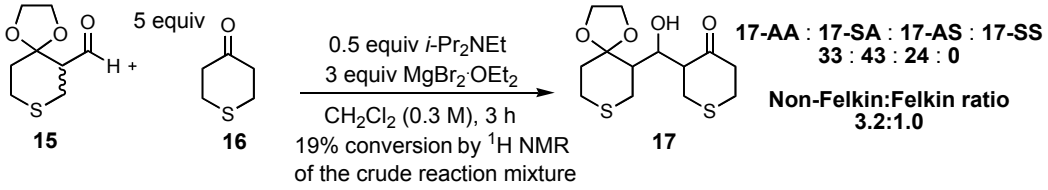


Figure 7. The effect of base on the $MgBr_2{\cdot}OEt_2$ promoted aldol reaction between **15** and **16**.

2.4. Aldol Reactions using Soft Enolization – Mono aldol formation

After further exploration of the aldol addition of **15** and **16**, it was determined that conversion with respect to the aldehyde did not accurately represent the yield of aldol adducts obtained. Thus, the starting aldehyde **15** and thiopyranone **16** were independently subjected to the reaction conditions to test the stability of these reagents over the course of the reaction. Within ten minutes, both aldehyde **15** and thiopyranone **16** had undergone reaction. Aldehyde **15** slowly decomposed under these conditions and several side products could be observed although none were identified. Under the same reaction conditions and in the absence of aldehyde **15**, thiopyranone **16** underwent a self-aldol condensation (Figure 8).

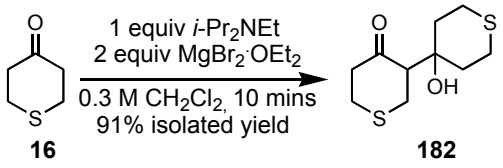


Figure 8. Self-aldol condensation of thiopyranone **16.**

To determine if the thiopyranone dimer **182** was formed reversibly, it was subjected to reaction with thiopyran aldehyde **15** under the same conditions. Aldol adducts **17** were obtained with yields and diastereoselectivites similar to those using **16**. Thus, the formation of the thiopyranone dimer **182** is reversible under the reaction conditions so there is no need to suppress its formation (Figure 9).

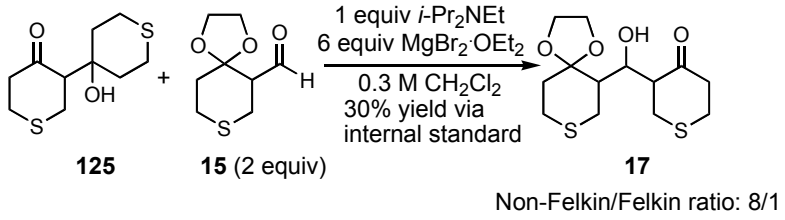


Figure 9. Determination of reversibility of thiopyranone-dimer **182**.

The stability of the aldol adducts was also examined. **17-SA** and **17-AS** were independently subjected to 1 equivalent of *i*-Pr_2NEt and 3 equivalents of $MgBr_2{\cdot}OEt_2$ in CH_2Cl_2 for 2.5 hours. Reaction of **17-SA** produced a small amount of **17-AA** indicating that a minor amount of isomerization had occurred but no products from retro-aldol could be detected (Figure 10). Similarly, reaction of **17-AS** gave a small amount of **17-SS** but no products from retro-aldol (Figure 10).

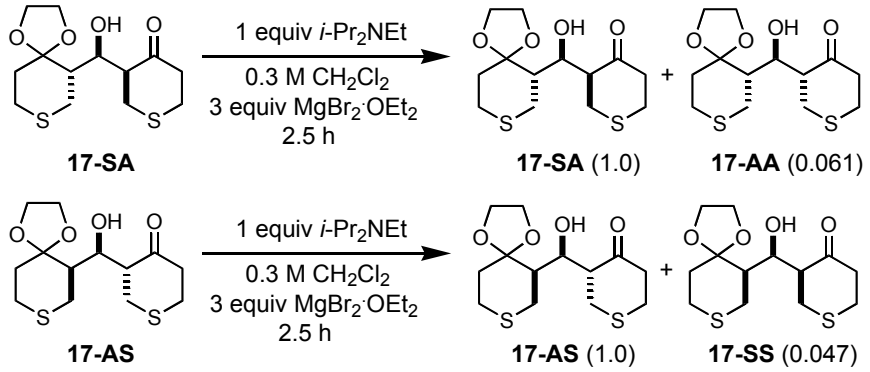


Figure 10. Stability of **17-SA** and **17-AS** to the aldol reaction conditions.

The reaction time was explored by removing aliquots at various time intervals. After ten minutes of reaction time, it was found that all the aldehyde had been consumed and the ratio of adducts was **17-AA** (53):**17-SA** (47) with numerous side products. Another aliquot taken after an hour yielded similar results, again no aldehyde **15** present and the ratio of diastereomers remained nearly constant at **17-AA** (51):**17-SA** (49) (Figure 11).

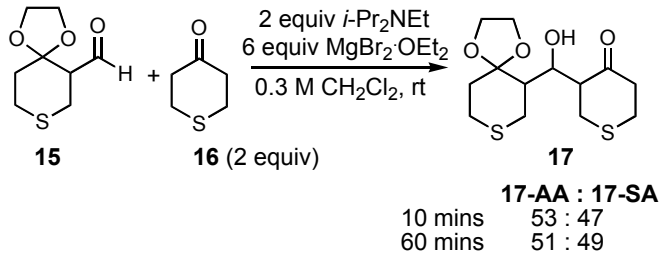


Figure 11. Completion of the $MgBr_2{\cdot}OEt_2$ promoted aldol addition of **15** and **16** determined by a time course study.

The order of addition of the reagents was next surveyed. Adding a solution of thiopyranone **16** to a solution of the other reagents drastically reduced the yield (3%) and non-Felkin/Felkin ratio (0/1) (Table 20, Entry 1). This could be attributed to the $MgBr_2 \cdot OEt_2$ and the *i*-Pr_2NEt forming a Lewis acid-base adduct leaving no *i*-Pr_2NEt available in solution to form the enolate. Similarly, adding a solution of thiopyranone **16** and *i*-Pr_2NEt to a solution of the other reagents also resulted in low yield (13%) and low non-Felkin/Felkin selectivity (3/1) (Table 20, Entry 2). When the *i*-Pr_2NEt was added over a period of 5 minutes to a solution of aldehyde **15**, thiopyranone **16**, and $MgBr_2 \cdot OEt_2$, the yield was 19% and non-Felkin/Felkin selectivity 7/1 (Table 20, Entry 3). When the *i*-Pr_2NEt was added rapidly, a similar yield and diastereoselectivity was achieved (Table 20, Entry 4). Thus, the rate of addition of the *i*-Pr_2NEt was determined to be inconsequential and the method of rapid addition was used for all subsequent experiments.

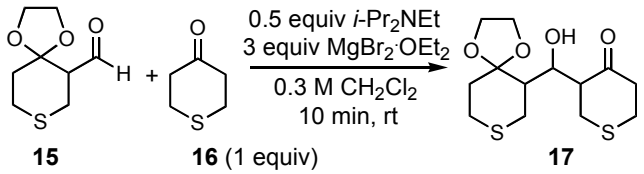


Table 20. Determination of the order of addition on the $MgBr_2 \cdot OEt_2$ promoted aldol reaction of **15** and **16**.

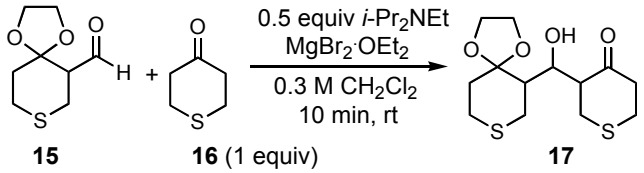
Entry	Order of addition	Yield (%) [b]	Diastereoselectivity [c] 17-AA : 17-SA : 17-AS : 17-SS	Non-Felkin/ Felkin [c]	17-SA : 17-AA [c]
1	**16** last over 1 min	3	0 : 0 : 0 : 100	0/1	0 : 0
2	**16** and *i*-Pr_2EtN last over 5 mins	13	30 : 45 : 0 : 24	3/1	1.0 : 1.5
3	*i*-Pr_2EtN last over 5 mins	19	35 : 51 : 6 : 7	7/1	1.0 : 1.5
4	*i*-Pr_2EtN last	24	35 : 54 : 5 : 6	8/1	1.0 : 1.5

[a] Reactions conducted on 0.10-mmol scale following the General Procedure for aldol reactions of **16** with **15** via Soft Enolization except where noted. [b] Determined via internal standard (1,4-

dicyanobenzene) by ^{1}H NMR of the crude reaction mixture. [c] Determined by ^{1}H NMR of the crude reaction mixture.

When the amount of $MgBr_2 \cdot OEt_2$ was increased from 3 to 6 equivalents, there was an increase in the non-Felkin/Felkin selectivity (Table 21). A 6-fold excess of $MgBr_2 \cdot OEt_2$ with respect to aldehyde **15** is enough to achieve high non-Felkin selectivity. As an additional benefit, these experiments demonstrate that this method produces a more favourable **17-SA**:**17-AA** ratio, allowing more direct access to the thermodynamically less stable **17-AA** diastereomer (the equilibrium constant is 2:1 in favour of **17-SA** over **17-AA**[8]).

Table 21. Effect of $MgBr_2 \cdot OEt_2$ on the diastereoselectivity of the aldol reaction between **15** and **16**



15 **16** (1 equiv) **17**

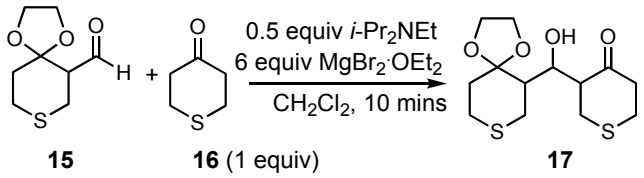
Entry	Equiv $MgBr_2 \cdot OEt_2$	Yield (%) [b]	Diastereoselectivity [c] 17-AA : 17-SA : 17-AS : 17-SS	Non-Felkin/ Felkin [c]	17-SA : 17-AA [c]
1	3	17	37 : 55 : 4 : 4	12/1	1.5 : 1.0
2	6	31	47 : 51 : 2 : 1	45/1	1.1 : 1.0

[a] Reactions conducted on 0.10-mmol scale following the General Procedure for aldol reactions of **16** with **15** via Soft Enolization except where noted. [b] Determined via internal standard (1,4-dicyanobenzene) by ^{1}H NMR of the crude reaction mixture. [c] Determined by ^{1}H NMR of the crude reaction mixture.

Lowering the temperature of the reaction from room temperature to 0 ^{o}C reduced the amount of side products formed without adversely affecting the yield or diastereoselectivity (Table 22). Reaction at -20 ^{o}C further reduced the amount of side products but also adversely affected the non-Felkin/Felkin selectivity and yield. At this reduced temperature, less chelated aldehyde versus non-chelated aldehyde could be present explaining the increase in Felkin products. Concentration effects were also probed (Table 22). At lower concentration, the

amounts of undesired side products were reduced. Beneficially, the non-Felkin/Felkin ratio increased as concentration decreased.

Table 22. Effect of concentration on the diastereoselectivity of $MgBr_2 \cdot OEt_2$ promoted aldol reaction between **15** and **16**



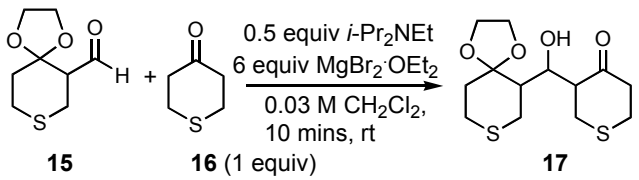
15 **16** (1 equiv) **17**

Entry	Conc CH_2Cl_2 (M)	Yield (%) [b]	Temp	Diastereoselectivity [c] 17-AA : 17-SA : 17-AS : 17-SS	Non-Felkin/ Felkin ratio [c]	17-SA : 17-AA [c]
1	0.9	28	rt	48 : 47 : 3 : 2	19/1	0.97 : 1.0
2	0.3	19	rt	45 : 50 : 3 : 2	19/1	1.1 : 1.0
3	0.1	26	rt	37 : 61 : 2 : 1	33/1	1.6 : 1.0
4	0.03	23	rt	42 : 56 : 2 : 0	49/1	1.3 : 1.0
5	0.01	23	rt	31 : 66 : 2 : 0	49/1	2.1 : 1.0
6	0.3	27	0°C	38 : 54 : 2 : 6	12/1	1.4 : 1.0
7	0.3	24	-20°C	29 : 65 : 1 : 4	18/1	2.2 : 1.0

[a] Reactions conducted on 0.10-mmol scale following the General Procedure for aldol reactions of **16** with **15** via Soft Enolization except where noted. [b] Determined via internal standard (1,4-dicyanobenzene) by ^{1}H NMR of the crude reaction mixture. [c] Determined by ^{1}H NMR of the crude reaction mixture.

The order of addition was again examined. It was found that the order of addition had a large impact on the ratio of **17-SA** and **17-AA** formed in the reaction. Adding the aldehyde **15** to a solution of *i*-Pr_2NEt, thiopyranone **16** and $MgBr_2 \cdot OEt_2$ resulted in a more favourable **17-SA**:**17-AA** ratio (0.9:1, Table 23, entry 2), allowing more direct access to the thermodynamically less stable **17-AA** diastereomer. Alternatively, adding aldehyde **15** pre-complexed with $MgBr_2 \cdot OEt_2$ resulted in the formation of numerous side products (Table 23, entry 3).

Table 23. Effect of order of addition on the diastereoselectivity of $MgBr_2 \cdot OEt_2$ promoted aldol reaction between **15** and **16**.



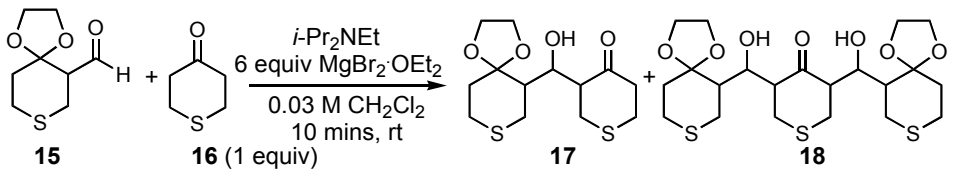
15 **16** (1 equiv) **17**

Entry	Order of addition	Yield (%) [b]	Diastereoselectivity [c] 17-AA : 17-SA : 17-AS : 17-SS	Non-Felkin/ Felkin [c]	17-SA : 17-AA [c]
1	*i*-Pr_2NEt last	36	34 : 64 : 2 : 1	35/1	1.9 : 1.0
2	Aldehyde **15** last	33	51 : 45 : 3 : 1	23/1	0.9 : 1.0
3	Aldehyde **15** last with 3 equiv's $MgBr_2 \cdot OEt_2$	34 [d]	50 : 47 : 3 : 0	28/1	0.93 : 1.0

[a] Reactions conducted on 0.10-mmol scale following the General Procedure for aldol reactions of **16** with **15** via Soft Enolization except where noted. [b] Determined via internal standard (1,4-dicyanobenzene) by ^{1}H NMR of the crude reaction mixture. [c] Determined by ^{1}H NMR of the crude reaction mixture. [d] Several side reactions occurring.

The effect of the amount of *i*-Pr_2NEt added was studied (Table 24). By increasing the number of equivalents of *i*-Pr_2NEt from 0.5 to 4.5 equivalents, the yield of all aldol adducts did not rise past the ca. 60% obtained with 1.5 equivalents of *i*-Pr_2NEt. When excess base is used, the amount of undesired side products increased. Additionally, regardless of the amount of base employed, 6 equivalents of $MgBr_2 \cdot OEt_2$ were sufficient to keep a high non-Felkin/Felkin ratio.

Table 24. Effect of the amount of *i*-Pr_2NEt on the yield and diastereoselectivity of the $MgBr_2 \cdot OEt_2$ promoted aldol reaction between **15** and **16.** [a]



Entry	Equiv *i*-Pr_2NEt	Yield (%) [b, d]	Diastereoselectivity [c, d] 17-AA : 17-SA : 17-AS : 17-SS	Non-Felkin/Felkin ratio [c]	17-SA : 17-AA [c]
1	0.5	26	39 : 59 : 2 : 0.5	39/1.0	1.5 : 1.0
2	1.5	59	57 : 41: 2 : 0	49/1.0	0.73 : 1.0
3	3	50	50 : 50 : 0 : 0	ND [d]	1.0 : 1.0
4	4.5	57	59 : 41 : ND : 0 [e]	ND [d]	0.69 : 1.0
5	1.5 [f]	82	57: 42 : 0 : 0	ND [d]	1.0 : 1.4
6	1.5 [g]	63	58 : 43 : 0 : 0	ND [d]	1.0 : 1.3

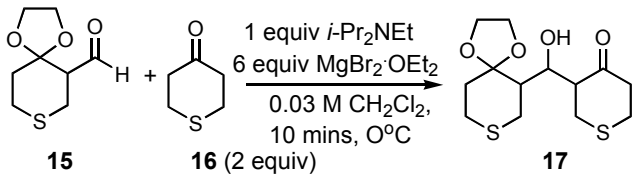
[a] Reactions conducted on 0.10-mmol scale following the General Procedure for aldol reactions of **16** with **15** via Soft Enolization except where noted. [b] Determined via internal standard (1,4-dicyanobenzene) by ^1H NMR of the crude reaction mixture. [c] Determined by ^1H NMR of the crude reaction mixture. [d] Significant overlap of mono-aldol and bis-aldol diastereomers. [e] Overlap of side products with **17-SS** and **17-AS**. [f] *i*-Pr_2NEt added fast. [g] *i*-Pr_2NEt added over 3 minutes.

The six reaction mixtures described in Table 24 were combined and the products were isolated. In addition to isolating 32% yield of **17** (as a 57:39:3:1 mixture of **17-AA**, **17-SA**, **17-AS** and **17-SS**, respectively), a mixture of bis-aldol adducts **18** (6% based on aldehyde) were also isolated. The latter was tentatively identified as a 1:1:2 mixture of three previously unknown bis-aldol **18-SA-trans-SA**, **18-AA-trans-AA**, **18-SA-trans-AA**, respectively. Isolating bis-aldols was disappointing as it revealed that signals for the bis-aldols overlap with the signals from the non-Felkin mono-aldol adducts in the ^1H NMR, complicating any efforts at further optimization. However, the formation of bis-aldols **18** was also promising because it was the first

demonstration that non-Felkin diastereoselectivity could be achieved in the aldol reaction of **17** with **15**.

Taken together, the above results suggest that the reaction at 0.03 M in aldehyde, with 2 equivalents of thiopyranone **16** and a 2:1 ratio of ketone **16** to *i*-Pr_2NEt was optimal. Under these conditions, the reaction resulted in good yield of aldol adducts (64% via internal standard) with a high non-Felkin/Felkin ratio (75/1) (Table 25, entry 1). Using the same conditions except adding the aldehyde to a solution of the other reactants resulted in a relative increase in the amount of the least thermodynamically stable **17-AA** diastereomer, although in low yield (Table 25, entry 2). When 0.2 equivalents of *i*-Pr_2NEt was used the conversion was lower than when one equivalent was used but a similar product ratio was obtained (entry 3, Table 25).

Table 25. Effect of order of addition on the diastereoselectivity and yield of the $MgBr_2 \cdot OEt_2$ promoted aldol reaction between **15** and **16**.



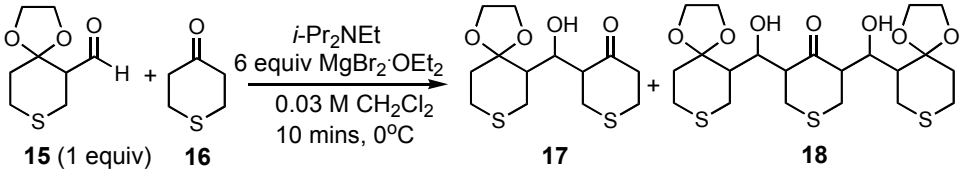
Entry	Order of Addition	Yield 17 (%) [a]	Diastereoselectivity [b] 17-AA : 17-SA : 17-AS : 17-SS	Non-Felkin/ Felkin [b]	17-SA : 17-AA [b]
1	*i*-Pr_2NEt last	64	38 : 61 : 1 : 0	75/1	1.6 : 1.0
2	**15** last	18	67 : 33 : 0 : 0 [c]	1/0	0.5 : 1.0 [c]
3	*i*-Pr_2NEt last [d]	32	33 : 67 : 0 : 0	1/0	2.1 : 1.0

[a] Reactions conducted on 0.10-mmol scale following the General Procedure for aldol reactions of **16** with **15** via Soft Enolization except where noted. [a] Determined via internal standard (1,4-dicyanobenzene) by ^{1}H NMR of the crude reaction mixture. [b] Determined by ^{1}H NMR of the crude reaction mixture. [c] Overlap of bis-aldol diastereomers **18**. [d] 0.2 equivalents of *i*-Pr_2NEt.

Larger scale reactions (0.5 mmol of **15**) were conducted under these conditions to obtain a 71% yield of **17-SA** and **17-AA** (Table 26, entry 1). Increasing the amount of the ketone

16/*i*-Pr_2NEt to 2.50/1.25 did not affect the yield of **17** or **18** but gave **17** with reduced stereoselectivity (Table 26, entry 2).

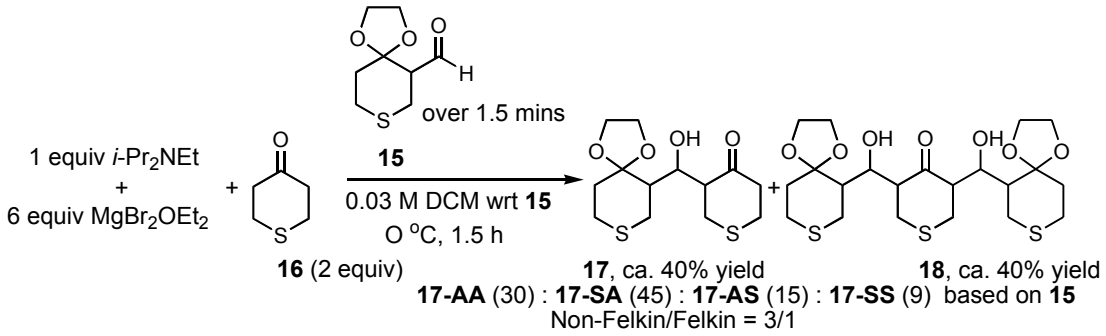
Table 26. Diastereoselectivity of $MgBr_2 \cdot OEt_2$ promoted aldol reactions of **15** and **16**



Entry	Equiv 16/ *i*-Pr_2NEt	Yield 17 (%) [b]	Diastereoselectivity [b] 17-AA : 17-SA : 17-AS : 17-SS	Yield 18 (%) [b,c]	Non-Felkin/ Felkin ratio [b]	17-SA : 17-AA [b]
1	2.0/1.0	71	31 : 68 : 0.6 : 0	10	160/1.0	2.2 : 1.0
2	2.50/1.25	70	44 : 53 : 2 : 0	12	44/1.0	1.2 : 1.0

[a] Reactions conducted on 0.52-mmol scale following the Procedure for Aldol Reactions of **16** with **15** via Soft Enolization except where noted. [b] Determined via isolation. [c] Based on **15**.

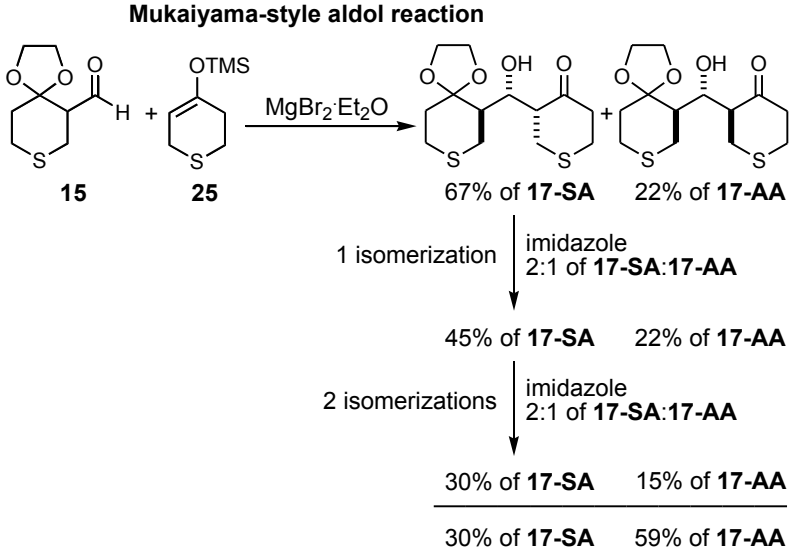
The protocol involving adding the aldehyde to a solution of the other reactants was also scaled-up. On scale, this reaction resulted in 40% yield and poor non-Felkin/Felkin diastereoselectivity, with significant bis-aldol formation (Scheme 26).



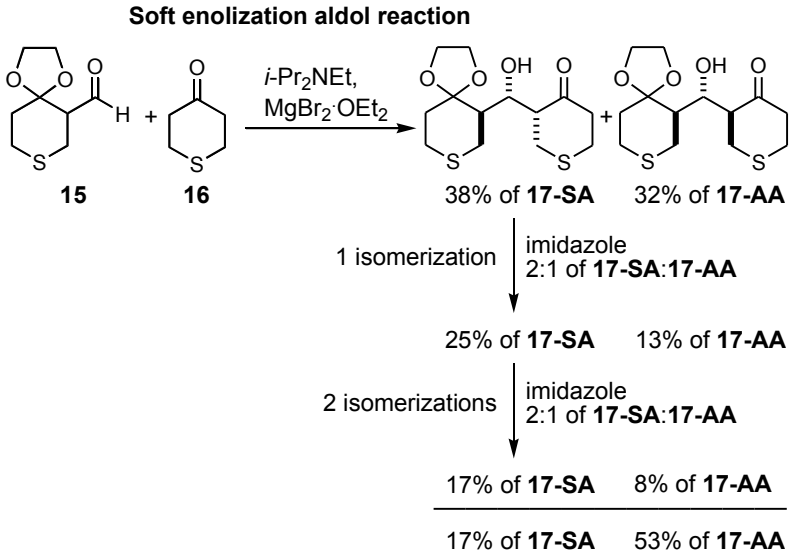
Scheme 26. Addition of **15** to a solution of the other reactants during the $MgBr_2 \cdot OEt_2$ promoted aldol addition of **15** and **16** on 0.5-mmol scale.

The above results show that the soft enolization methodology can be applied to the aldol reaction of aldehyde **15** and ketone **16** to produce the non-Felkin adducts **17-SA** and **17-**

AA in 70% yield. A drawback to this method is the competitive formation of bis-aldol adducts. As reported previously, the $MgBr_2 \cdot OEt_2$-mediated aldol reaction of **25** with **15** results in 61% of **17-SA** after one crystallization and a 4:1 mixture of **17-AA**:**17-SA** that can be fractionated to give 6% **17-SA** and 22% **17-AA** (89% isolated yield of aldol adducts).[7] Isomerization of the **17-SA** in 1 M imidazole in CH_2Cl_2 after one day yields a 2:1 mixture of **17-SA**:**17-AA** in 98% yield.[8] After 2 cycles of isomerization, 59% of **17-AA** can be obtained (Scheme 27). Comparing this to the soft enolization methodology developed here, after one reaction and 2 isomerization cycles, 53% **17-AA** can be obtained (Scheme 28). Thus, the two methods are comparable for access to the **17-AA** diastereomer however the Mukaiyama style aldol reaction has been performed on larger scale (5.74 mmol reported) and is superior for access to the **17-SA** diastereomer.



Scheme 27. Yield of **17-SA** and **17-AA** after the Mukaiyama style aldol reaction of **15** and **25** followed by 2 isomerization reactions.



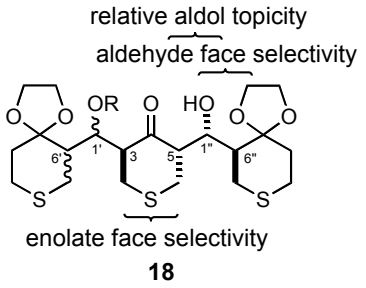
Scheme 28. Yield of **17-SA** and **17-AA** after the soft enolization aldol reaction of **15** and **16** followed by 2 (hypothetical) isomerization reactions.

2.5. Aldol Reactions using Soft Enolization – Bis-aldol formation

After exploration of the $MgBr_2{\cdot}OEt_2$ promoted aldol reaction of **15** with **16**, the soft enolization methodology was applied to the aldol reaction of **15** with **17**. An aldol reaction of **15** with **17** can produce twenty unique bis-aldol diastereomers **18**, six of which had not been previously synthesized. These six unknown diastereomers all share the common feature of 1',6' anti and 1'', 6'' anti relative configurations (Scheme 18); they can arise from non-Felkin additions to **17-SA** and **17-AA**. The 1',6' anti configuration is strongly favoured under the soft enolization conditions in the aldol addition of **15** and **16** producing selectively **17-SA** and **17-AA**. It was hypothesized that applying the same methodology to the reactions of **15** with **17-SA** and **17-AA** would have the potential to generate any of the remaining unknown bis-aldol **18** diastereomers.

Aldol reactions of chiral reactants such as **17** and **15** exhibit three stereocontrol elements: aldol relative topicity, enolate face selectivity and aldehyde face selectivity (Figure

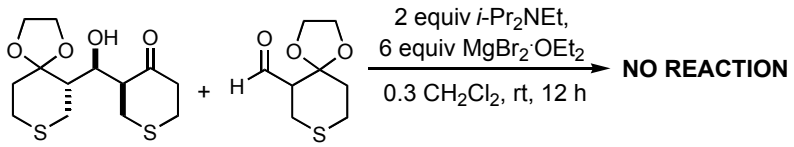
12). With respect to the TR2P, the relative topicity (5,1''-syn or 5,1''-anti) of the aldol coupling can be controlled by employing titanium or boron enolates of **17**. The diastereoface selectivity of the ketone enolate is governed by the nature of the protecting group on the C-1' hydroxyl group. β-alkoxy ketones (Figure 12, R=MOM, Et_3Si, or Ac) generally undergo aldol reactions to give 3,5-*trans* products while β-hydroxy ketones (Figure 12, R=H) under certain conditions undergo aldol reactions to give 3,5-cis products. Aldehyde **15** strongly favours Felkin diastereoface selectivity (1'',6''-*syn* relative configuration). In the reaction with **16**, non-Felkin diastereoface selectivity can be achieved in the presence of $MgBr_2 \cdot OEt_2$. However, prior to this work, all attempts to obtain non-Felkin diastereoface selectivity in the aldol reaction of **15** with **17** had failed.



18

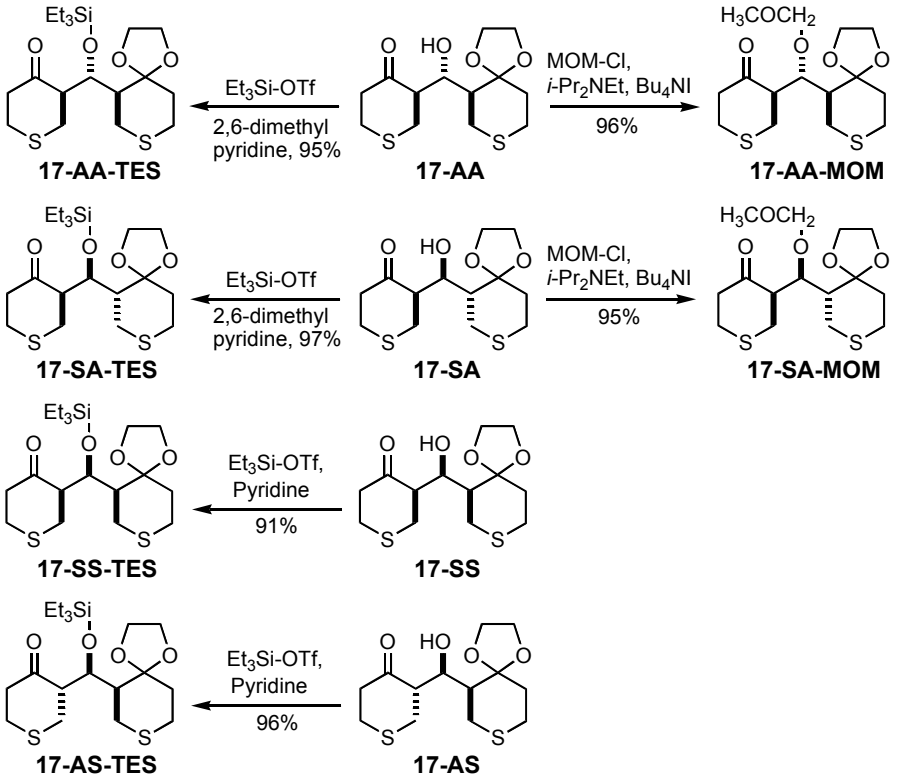
Figure 12. Relationship between the relative configuration of bis-aldol adduct **18** and the underlying three stereocontrol elements.

The soft enolization reaction chemistry was first explored with **17-SA**. No reaction occurred when the free alcohol was present (Figure 13). Protecting the alcohol was necessary and the two protecting groups chosen for study were methoxymethyl (MOM) and triethylsilyl (TES) as these derivatives were previously utilized successfully in the TR2P (Scheme 29).



17-SA (2 equiv) **15**

Figure 13. Failed $MgBr_2 \cdot OEt_2$ promoted aldol reaction between **17-SA** and **15**.



Scheme 29. Protection of mono-aldol adducts **17** with MOM and TES protecting groups.[8, 10]

The aldol addition of **15** and **17** was explored initially using the conditions optimized for the aldol reaction of **15** with **16**. The first substrate examined was **17-SA-TES**. Using one equivalent each of *i*-Pr_2NEt, aldehyde **15** and ketone **17-SA-TES**, 6 equivalents of $MgBr_2 \cdot OEt_2$, at 0 ^oC in CH_2Cl_2 resulted in a highly diastereoselective aldol addition where only 2 of 8 possible diastereomers were detected in moderate yield (Entry 1, Table 27). Both of the products had trans relationship across the middle ring (3,5-trans) and arose from non-Felkin addition to aldehyde **15** (1'', 6''-anti), however they differed in their relative aldol topicity (5,1''-syn versus 5-1''-anti). The syn aldol **18-SA-TES-trans-SA** was favoured over the anti aldol **18-SA-TES-trans-AA** by 2.5:1. As was the case with the $MgBr_2 \cdot OEt_2$ promoted aldol addition of **15** and **16**, doubling the amount of *i*-Pr_2NEt did not improve the yield and the diastereoselectivity remained the same (Entry 2, Table 27).

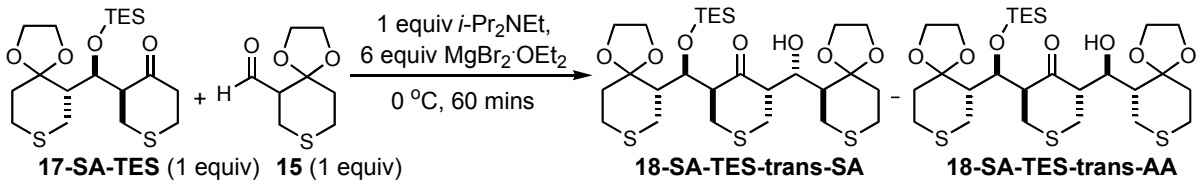
Concentration effects were explored for the **17-SA-TES** substrate (Table 27, Entry 1, 3, 4). Higher concentration disfavoured formation of the product. Moreover, a marked difference

in the diastereoselectivity was observed at higher concentration, nearly 6:1 ratio in favour of the syn aldol product **18-SA-TES-trans-SA**, however the yield was dramatically reduced (Table 27, Entry 4). The highest yield was obtained with a 0.03 M solution, therefore this concentration was employed for all other experiments (Table 27, Entry 1). Changing the order of addition by adding the ketone **17-SA-TES** last resulted in a similar yield as adding the base last (Table 27, entry 5).

The yield of the aldol addition of **15** with **17-SA-TES** was moderate, therefore two other bases were tried. No reaction occurred using pyridine as the base. The use of 2,6-lutidine could promote an aldol addition under these conditions, albeit in much lower yield than *i*-Pr_2NEt (Table 27, entry 6, 7).

On scaling up, the aldol addition of **15** with **17-SA-TES** gave a combined 68% yield of the two bis-aldols diastereomers **18-SA-TES-trans-SA** and **18-SA-TES-trans-AA**. This yield was higher than expected judging from the experiments performed on smaller scale (Table 27, Entry 1 vs Entry 8).

Table 27. Diastereoselectivity of $MgBr_2 \cdot OEt_2$ promoted aldol reaction between **15** and **17-SA-TES**



Entry	Conc CH_2Cl_2 (M)	Yield (%) [a, b]	Diastereoselectivity [a] 18-SA-TES-trans-SA : 18-SA-TES-trans-AA
1	0.03	49	2.5 : 1.0
2 [c]	0.03	31	2.5 : 1.0
3	0.01	41	2.4 : 1.0
4	0.09	12	5.9 : 1.0
5 [d]	0.03	54	3.0 : 1.0
6 [e]	0.03	0	-
7 [f]	0.03	22	4.8 : 1.0
8 [g]	0.03	68 [h]	3.5 :1.0

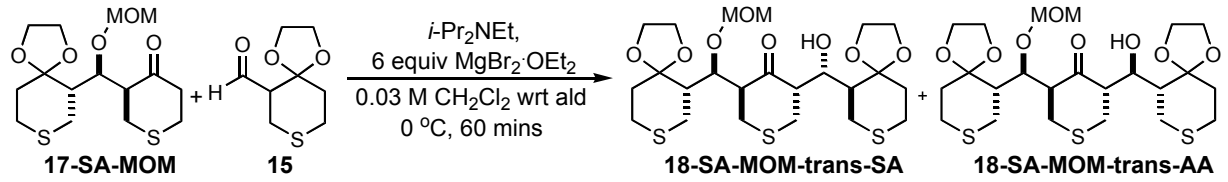
[a] Determined via internal standard (1,4-dicyanobenzene) by ^{1}H NMR of the crude reaction mixture. [b] Combined yields via internal standard of both diasteromers of **18**. [c] 2 equivalents of *i*-Pr_2NEt. [d] Addition of ketone last. [e] Pyridine used as the base. [f] 2,6-Lutidine as the base. [g] 100 mg of **17-AS-TES**. [h] Combined isolated yield of both diastereomers of **18**.

Reaction of **15** with **17-SA-MOM** gave similar results to those obtained with **17-SA-TES**. Using one equivalent each of *i*-Pr_2NEt, aldehyde **15** and ketone **17-SA-MOM**, 6 equivalents of $MgBr_2 \cdot OEt_2$, at 0 ^{o}C in CH_2Cl_2 resulted in a highly diastereoselective aldol addition where only 2 of 8 possible diastereomers were detected in low yield (entry 1, Table 28). As with the **17-SA-TES** substrate, both products had a trans relationship across the middle ring (3,5-trans) and

arose from non-Felkin addition to **15** (1'', 6''-anti), however they differed in their relative configuration (5,1''-syn versus 5,1''-anti).

Examinations of the stoichiometry and reaction time were conducted for the reaction of **15** with **17-SA-MOM**. Changing the excess reactant from aldehyde **15** to ketone **17-SA-MOM** or *i*-Pr_2NEt only resulted in minor changes in the yield and diastereoselectivity. In all cases, the yields were less than 40% with close to 1:1 diastereoselectivity (Table 28).

Table 28. Diastereoselectivity of $MgBr_2 \cdot OEt_2$ promoted aldol reaction between **15** and **17-SA-MOM** at various stoichiometries

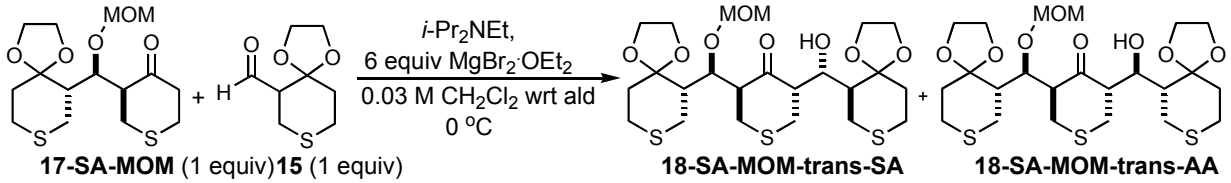


Entry	Ald 15 (equiv)	17-SA-MOM (equiv)	Equiv *i*-Pr_2NEt	Yield (%) [a, b]	Diastereoselectivity [a] 18-SA-trans-SA : 18-SA-trans-AA
1	1	1	1	38	1.0 : 1.2
2	2	1	1	25	1.3 : 1.0
3	1	2	1	30	1.0 : 1.3
4	1	1	2	37	1.1 : 1.0

[a] Determined via internal standard (1,4-dicyanobenzene) by ^{1}H NMR of the crude reaction mixture. [b] Combined yield via internal standard of both diastereomers of **18**.

A time course study was performed on the reaction of **15** with **17-SA-MOM** to determine the optimal reaction time (Table 29). The reaction reached a maximum completion within ten (35% yield) and the yield slowly decreased with increasing reaction time, suggesting that the bis-aldol products **18-SA-MOM-trans-SA** and **18-SA-MOM-trans-AA** are not indefinitely stable to the reaction conditions.

Table 29. Diastereoselectivity of $MgBr_2 \cdot OEt_2$-promoted aldol reaction between **15** and **17-SA-MOM** at various reaction times

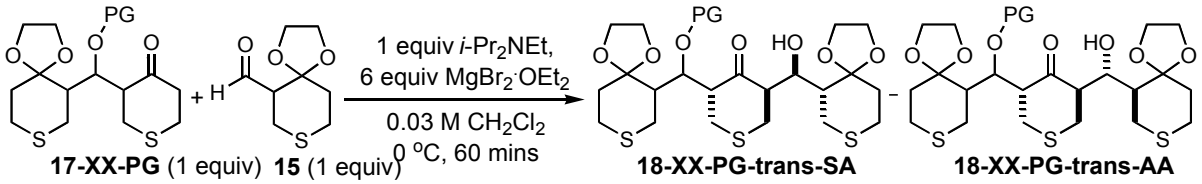


Entry	Time (min)	Yield (%) [a, b]	Diastereoselectivity [a]
			18-SA-trans-SA : 18-SA-trans-AA
1	10	35	1.0 : 1.6
2	60	27	1.0 : 2.0
3	120	25	1.0 : 2.0

[a] Determined via internal standard (1,4-dicyanobenzene) by ^{1}H NMR of the crude reaction mixture. [b] Combined yield via internal standard of both diastereomers of **18**.

Taken together, the above results from the reactions of **15** with **17-SA-TES** and **17-SA-MOM** suggest that a short reaction time is important, with an initial aldehyde concentration of 0.03 M and with equimolar amounts of aldehyde, ketone and base. $MgBr_2 \cdot OEt_2$ promoted aldol reactions of **15** with **17-AA-TES**, **17-AA-MOM**, **17-AS-TES** and **17-SS-TES** were also examined and the results are collected in Table 30.

Table 30. Results of the $MgBr_2 \cdot OEt_2$-promoted aldol reaction between **15** and **17-AA-TES**, **17-AA-MOM**, **17-AS-TES**, or **17-SS-TES**



Entry	Ketone diastereomer	PG	Yield (%) [a, b]	Diastereoselectivity [a]
				18-XX-PG-trans-AA : 18-XX-PG-trans-SA
1	AA	TES	31	1.8 : 1.0

2 [c]	AA	TES	45 [f]	1.8 : 1.0
3	AA	MOM	n.d.	n.d.
4 [d]	AS	TES	66 [f]	1.5 : 1.0
5 [e]	SS	TES	27 [f]	1.0 : 1.0

[a] Determined via internal standard (1,4-dicyanobenzene) by ^{1}H NMR of the crude reaction mixture. [b] Combined yield via internal standard of both diastereomers of **18**. [c] 200 mg scale. [d] Reaction time 15 minutes. [e] Reaction time 30 minutes. [f] Combined isolated yield of both diastereomers of **18**.

As was observed for the reaction with **17-SA-TES**, scaling up the reaction of **15** with **17-AA-TES** resulted in a slightly higher yield than what was expected from the reactions performed on small scale (Table 30, Entries 1 and 2). Again, only 2 of 8 possible diastereomers were detected; both resulted from trans addition to the enolate and non-Felkin addition to the aldehyde but they differed in relative aldol topicity (5,1''-syn versus 5,1''-anti). Unlike the **17-SA-TES** substrate, eliminated products as well as other side products were detected. Interestingly, the reaction of **15** with **17-AA-MOM** yielded dramatically different results than all the other substrates explored (Table 30, entry 3). Instead of producing two diastereomers as in the other substrates investigated, multiple inseparable products were generated. Further reactions of this substrate were not explored. Aldol reactions of aldehyde **15** with **17-SS-TES** and **17-AS-TES** were also conducted (Table 30, entry 4 and 5). In each case, only 2 of 8 possible diastereomers were formed. Both resulted from trans addition to the enolate and non-Felkin addition to the aldehyde but differ in 5,1''-syn versus 5,1''-anti relative aldol topicity.

Substrates examined for the second aldol reaction were: **17-SA-TES**, **17-SA-MOM**, **17-AA-TES, 17-AA-MOM**, **17-AS-TES** and **17-SS-TES**. Reactions employing the soft enolization conditions on the second aldol reaction of the TR2P resulted in high diastereoselectivity (only 2 of 8 possible diastereomers detected) in moderate to low yields except for the **17-AA-MOM** substrate. Conditions explored to increase the yields of the bis-aldol adducts included varying 1) the relative amounts of base, starting ketone **17**, and aldehyde **15**, 2) the nature of the amine base, 3) the concentration, and 4) the reaction time. None of these parameters increased the yields of the bis-aldol adducts to any significant extent. In addition to the moderate to low

yields, there was low recovery of the starting materials (ketone **17** and aldehyde **15**). When the protected ketones were subjected to the reaction conditions in the absence of aldehyde, only 64% of the ketone was recovered after work-up and the fate of the consumed starting material could not be determined. Thus, optimization efforts were discontinued because the reaction performed in this way allows too many uncontrollable side reactions that compete with product yield and starting material recovery. Nevertheless, the soft enolization methodology gave access to 3 previously unknown bis-aldol diastereomers (after deprotection: **17-AA-TES-trans-AA**, **17-SA-TES-trans-SA** [**17-SA-MOM-trans-SA**], and **17-AA-TES-trans-SA** = **17-SA-TES-trans-AA** [**17-SA-MOM-trans-AA**]). However, an improved method will be required to access synthetically useful amounts of these materials.

2.6. Determination of configuration of aldol diastereomers of 18

To confirm the relative configurations of the bis-aldol diastereomers of **18** produced in the above reaction, the protecting groups of the aldol adducts were removed. The number of resonances in the ^{13}C NMR gives key pieces of information regarding the symmetry of the bis-aldols. Of the twenty diastereomers of **18**, there are 4 C_s, 4 C_2 and 12 C_1 symmetric bis-aldols; by determining the symmetry, the number of candidate diastereomers for a given isomer is reduced. Unsymmetrical bis-aldol adducts (C_1) have 21 resonances in the ^{13}C NMR while symmetric adducts (C_2, C_s) only have 11 resonances. Symmetric bis-aldols can be either C_2 or C_s symmetrical and they can be distinguished from each other by reduction to the corresponding triol. C_s symmetric bis-aldols will give C_s symmetric triols while C_2 symmetric bis-aldols will reduce to give unsymmetrical triols (Figure 14).

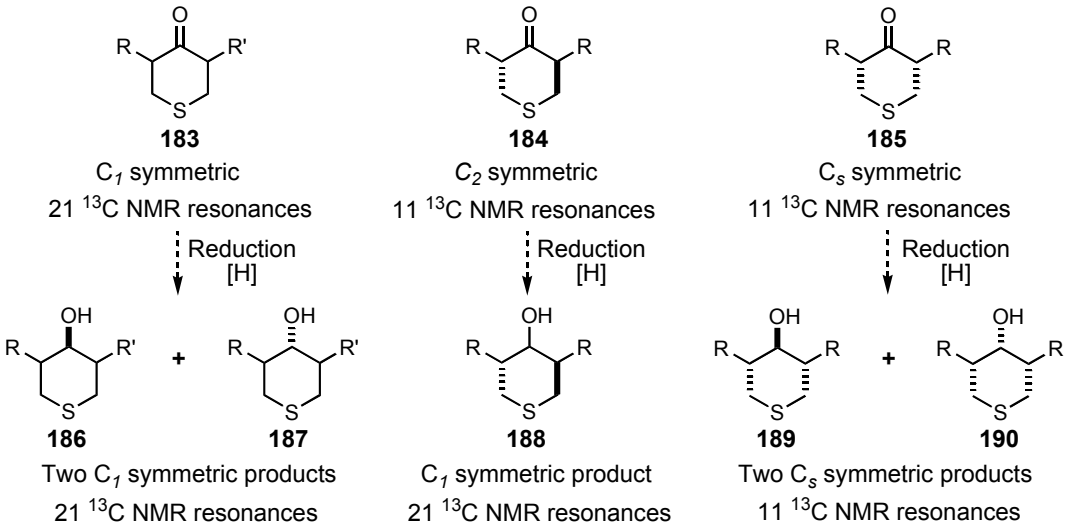


Figure 14. Symmetry relationship between bis-aldol adduct and subsequent triol for structure determination.

As shown in the introduction, β-hydroxy ketones (both from mono-aldol adducts **17** and bis-aldol adducts **18**) from the TR2P isomerize in the presence of imidazole. Isomerization of bis-aldols **18** also can be used to aid in structure determination. Additionally, isomerization can also be used to generate the three remaining unknown bis-aldols (**18-SA-cis-SA**, **18-AA-cis-AA**, **18-SA-cis-AA**) that could not be formed directly from the soft enolization methodology.

2.6.1. Bis-aldol 18-SA-TES-trans-SA and 18-SA-MOM-trans-SA

The adduct **18-SA-TES-trans-SA** was obtained as the major product both from the aldol reaction of **17-SA-TES** with **15** and the adduct **18-SA-MOM-trans-SA** from the aldol reaction of **17-SA-MOM** with **15** (Figure 15). The vicinal coupling constants between H_2C-2 and HC-3 (7 and 10 Hz) and between HC-5 and H_2C-6 (5 and 12 Hz) in the ^1H NMR spectrum of **18-SA-TES-trans-SA** suggests a trans 3,5-disubstituted thiopyranone ring in a twist-boat conformation. This compound also exhibits unique properties in the ^{13}C NMR; carbons C-2 and C-6 have chemical shifts of 23.8 and 22.1 ppm respectively, which are around 4 ppm upfield from "normal" and again consistent with an unusual conformation. Analysis of the vicinal coupling constants between H_2C-2 and HC-3 (7 and 9.5 Hz) and between HC-5 and H_2C-6 (5.5 and 11.5 Hz) in the ^1H NMR spectrum of **18-SA-MOM-trans-SA** indicate that the substituents at positions C-3 and C-5

of the thiopyranone ring were *trans* and that the conformation was unusual. Additionally, the X-ray crystal structure of **18-SA-MOM-trans-SA** confirmed the twist-boat conformation observed in the ^{1}H NMR spectrum (Figure 16).

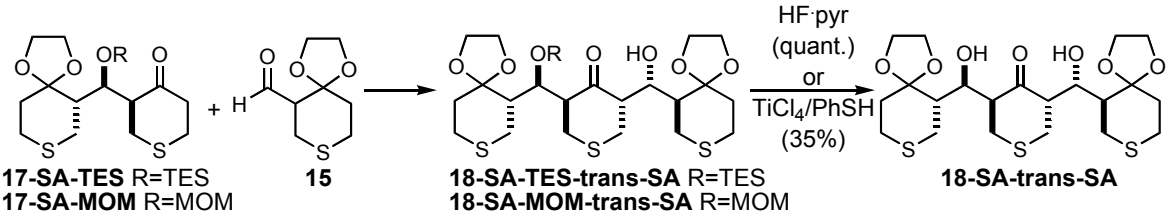


Figure 15. Determination of the relative configuration of **18-SA-TES-trans-SA** and **18-SA-MOM-trans-SA**.

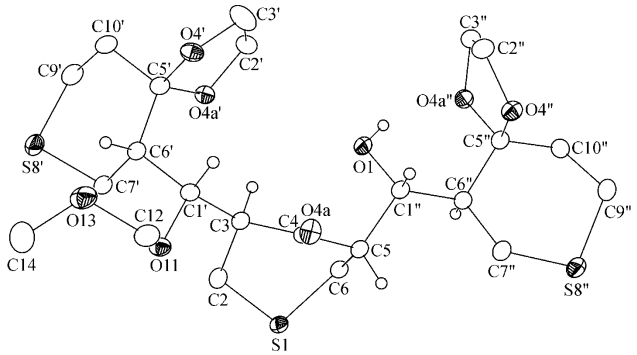


Figure 16. X-ray crystal structure determination of relative configuration of **18-SA-MOM-trans-SA**.

2.6.2. Bis-aldol 18-SA-trans-SA

Removal of the silyl protecting group in **18-SA-TES-trans-SA** by treatment with HF·pyridine/pyridine and of the MOM ether in **18-SA-MOM-trans-SA** by treatment with $TiCl_4$/PhSH gave the bis-aldol **18-SA-trans-SA** in quantitative and 35% yields respectively (Figure 15). This adduct is symmetric as indicated by the presence of only 11 resonances in the ^{13}C NMR spectrum. Symmetric bis-aldol adducts can be C_s or C_2 symmetric. These possibilities can be distinguished by reduction to the triol as C_s symmetric bis-aldols will give symmetric triols (as indicated by 11 resonances in the ^{13}C NMR spectrum) while C_2 bis-aldols will produce non-symmetric triols (as indicated by 21 resonances in the ^{13}C NMR spectrum). Reduction of **18-SA-trans-SA** with $NaBH_4$ gave the unsymmetric triol **191** (40% isolated yield[3]). The triol was

[3] Low isolated yield due to incomplete removal of the salts formed during the reaction.

unsymmetric as indicated by the presence of 21 resonances in the ^{13}C NMR spectrum; this result indicates that **18-SA-trans-SA** was a C_2 symmetric bis-aldol adduct. Of the twenty possible bis-aldol diastereomers, there are 4 C_s, 4 C_2 and 12 C_1 symmetric bis-aldols. The structure of **18-SA-trans-SA** is established because of the four C_2 symmetric bis-aldol adducts possible, only one can result from an aldol reaction of **17-SA-TES** or **17-SA-MOM**.

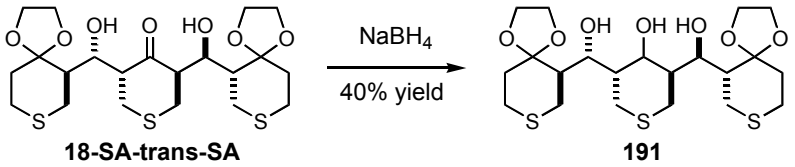


Figure 17. Reduction of the symmetric diol **18-SA-trans-SA** to an unsymmetric triols confirms the diol is C_2 symmetric.

The structure of **18-SA-trans-SA** was further confirmed by imidazole catalyzed isomerization (Figure 18). A solution of **18-SA-trans-SA** in 0.3 M imidazole in $CDCl_3$ was prepared and monitored by ^1H NMR. An equilibrium mixture of **18-SA-cis-AA** (47%), **18-SA-trans-SA** (26%) and **18-AA-trans-AA** (26%) was found after 11 days.

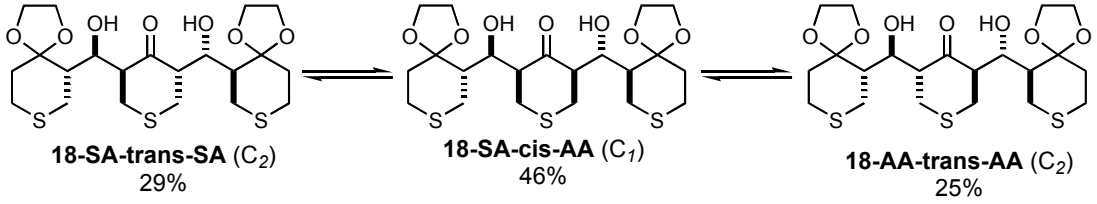


Figure 18. Isomerization of **18-SA-trans-SA** with 0.3 M imidazole in $CDCl_3$.

2.6.3. Bis-aldol 18-AA-TES-trans-AA

The adduct **18-AA-TES-trans-AA** was obtained as the major product from the aldol reaction of **17-AA-TES** with **15** (Figure 19). The vicinal coupling constants between H_2C-2 and HC-3 (5, 5.5 Hz) in the ^1H NMR spectrum of **18-AA-TES-trans-AA** indicated that the substituents at positions C-3 and C-5 of the thiopyranone ring were *trans*. The structure of **18-AA-TES-trans-AA** was assigned based on its deprotection product **18-AA-trans-AA**.

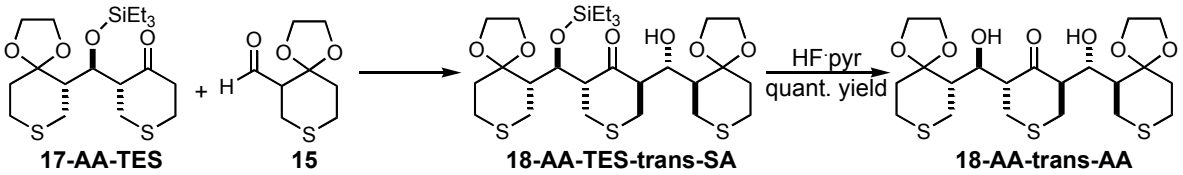


Figure 19. Determination of the relative configuration of **18-AA-TES-trans-AA**.

2.6.4. Bis-aldol 18-AA-trans-AA

Removal of the silyl protecting group in **18-AA-TES-trans-AA** under HF·pyridine/pyridine conditions gave **18-AA-trans-AA** in quantitative yield (Figure 19). This adduct is symmetric as indicated by the presence of only 11 resonances in the ^{13}C NMR spectrum. Symmetric bis-aldol adducts can be C_s or C_2 symmetric. They can be distinguished from each other by reduction to the triol as C_s symmetric adducts will give symmetric triols (as indicated by 11 resonances in the ^{13}C NMR spectrum) while C_2 adducts will reduce to non-symmetric triols (as indicated by 21 resonances in the ^{13}C NMR spectrum). Reduction of **18-AA-trans-AA** with $NaBH_4$ gave the unsymmetric triol **191** (89% isolated yield). The triol was unsymmetric as indicated by the presence of 21 resonances in the ^{13}C NMR spcectrum; this result indicates that **18-AA-trans-AA** was a C_2 symmetric bis-aldol adduct. Of the twenty bis-aldol diastereomers, there are 4 C_s, 4 C_2 and 12 C_1 symmetric bis-aldols. The structure of **18-AA-trans-AA** is established because of the four C_2 symmetric bis-aldol adducts possible, only one can result from an aldol reaction of **17-AA-TES**. Additionally, with the obtention of **18-SA-trans-SA** and **18-AA-trans-AA** all 4 possible C_2 symmetric bis-aldols **18** are known: one from each of the 4 possible diastereomers **17**.

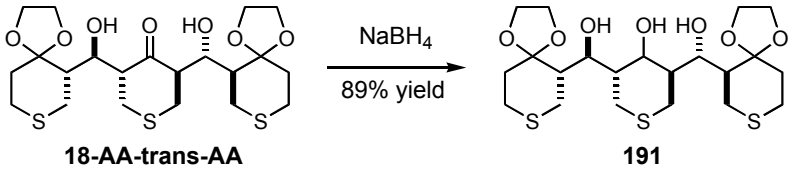


Figure 20. Reduction of the symmetric diol **18-AA-trans-AA** to an unsymmetric triol confirms the diol is C_2 symmetric.

The structure of **18-AA-trans-AA** was further confirmed by imidazole catalyzed isomerization. In 0.3 M imidazole in $CDCl_3$, an equilibrium mixture of **18-SA-cis-AA** (46%), **18-SA-trans-SA** (29%) and **18-AA-trans-AA** (25%) was obtained after 3 days (Figure 21).

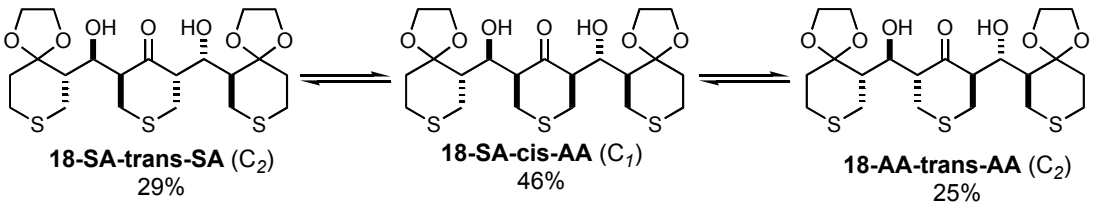


Figure 21. Isomerization of **18-AA-trans-AA** with 0.3 M imidazole in $CDCl_3$.

2.6.5. Bis-aldol 18-SA-TES-trans-AA and 18-SA-MOM-trans-AA

The adduct **18-SA-TES-trans-AA** was obtained as the minor product from the aldol reaction of **17-SA-TES** with **15**; the adduct **18-SA-MOM-trans-AA** was obtained from the aldol reaction of **17-SA-MOM** with **15** (Figure 22). The vicinal coupling constants between H_2C-2 and HC-3 (8 and 8 Hz, respectively) and between HC-5 and H_2C-6 (4 and 8 Hz, respectively) in the ^1H NMR spectrum of **18-SA-TES-trans-AA** indicate a trans 3,5-disubstituted thiopyranone ring. An X-ray crystal structure of **18-SA-TES-trans-AA** confirmed the stereochemical assignment (Figure 23). Analysis of the vicinal coupling constants between H_2C-2 and HC-3 (6.5 and 10.5 Hz, respectively) and between HC-5 and H_2C-6 (5 and 9 Hz, respectively) in the ^1H NMR spectrum of **18-SA-MOM-trans-AA** indicated that the substituents at positions C-3 and C-5 of the thiopyranone ring were *trans*. The structure of **18-SA-MOM-trans-AA** was assigned based on its deprotection product **18-SA-trans-AA**.

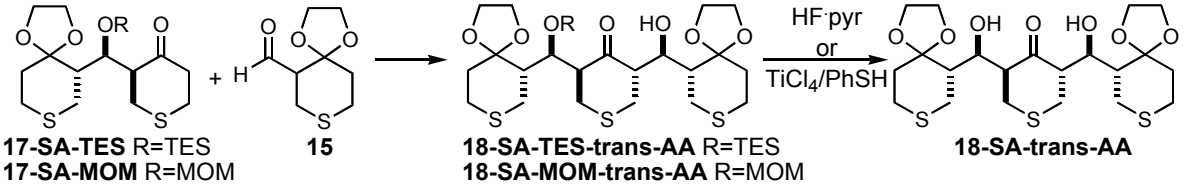


Figure 22. Determination of the relative configuration of **18-SA-TES-trans-AA** and **18-SA-MOM-trans-AA**.

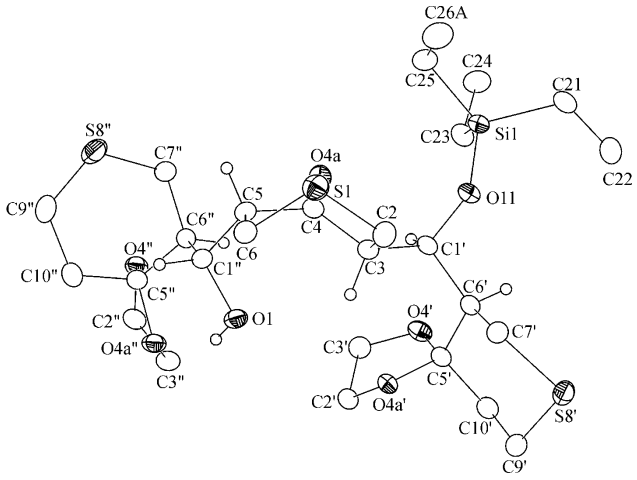


Figure 23. X-ray crystal structure determination of relative configuration of **18-SA-TES-trans-AA**.

2.6.6. Bis-aldol 18-SA-trans-AA (=18-AA-trans-SA)

Removal of the silyl protecting group in **18-SA-TES-trans-AA** by reaction with HF·pyridine/pyridine and the MOM ether in **18-SA-MOM-trans-AA** by reaction with $TiCl_4$/PhSH gave **18-SA-trans-AA** (=**18-AA-trans-SA**) in 93% and 57% conversions (determined from the ^{1}H NMR spectrum), respectively (Figure 22). This adduct is unsymmetrical as indicated by the presence of 21 resonances in the ^{13}C NMR spectrum. The structure of **18-SA-trans-AA** is inferred from that of the precursor **18-SA-TES-trans-AA** (X-ray). The structure of **18-SA-trans-AA** is further confirmed because the same adduct is obtained from deprotection of **18-AA-TES-trans-SA** and isomerization gives 2 C_s symmetric bis-aldols (vide infra).

2.6.7. Bis-aldol 18-AA-TES-trans-SA

The adduct **18-AA-TES-trans-SA** was obtained as the minor product from the aldol reaction of **17-AA-TES** with **15** (Figure 24). The coupling constants of HC-3 (ddd, 5, 5 and 5 Hz) in the ^{1}H NMR of **18-AA-TES-trans-SA** indicates that the substituents at positions C-3 and C-5 of the thiopyranone ring were *trans*; the HC-5 peak was buried and the HC-6 was strongly coupled. The structure of **18-AA-TES-trans-SA** is assigned based on its deprotection product **18-AA-trans-SA** (vide infra, section 2.6.8).

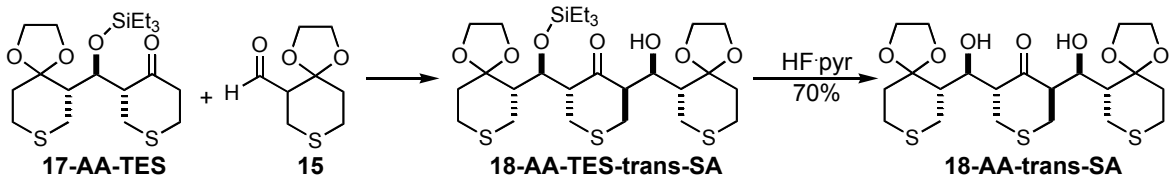


Figure 24. Determination of the relative configuration of **18-AA-TES-trans-SA**.

2.6.8. Bis-aldol 18-AA-trans-SA (=18-SA-trans-AA)

Removal of the triethylsilyl protecting group in **18-AA-TES-trans-SA** by treatment with HF·pyridine/pyridine conditions gave **18-AA-trans-SA** (=**18-SA-trans-AA**) in 70% yield (Figure 24). This adduct is unsymmetrical as indicated by the presence of 21 resonances in the ^{13}C NMR spectrum and is identical to the product **18-SA-trans-AA** described previously. The structure of **18-AA-trans-SA** (=**18-SA-trans-AA**) is established because of the twelve C_1 symmetric bis-aldol adducts possible, only one can be trans across the ring and result from deprotection of aldol adducts from reaction of **15** with **17-AA-TES** and **17-SA-TES** and **17-SA-MOM**.

The imidazole-catalyzed isomerization of bis-aldol **18-SA-trans-AA** was examined. The isomerization of **18-SA-trans-AA** in 0.3 M imidazole in $CDCl_3$ gave an equilibrium mixture in 2-3 days with the **18-SA-trans-AA** diastereomer predominating (46%), and two previously unknown C_s compounds **18-SA-cis-SA** (43%) and **18-AA-cis-AA** (11%) (Figure 25). Only **18-SA-trans-AA** could isomerize via enolization to produce **18-SA-cis-SA** and **18-AA-cis-AA**, firmly establishing the relative configuration of this adduct.

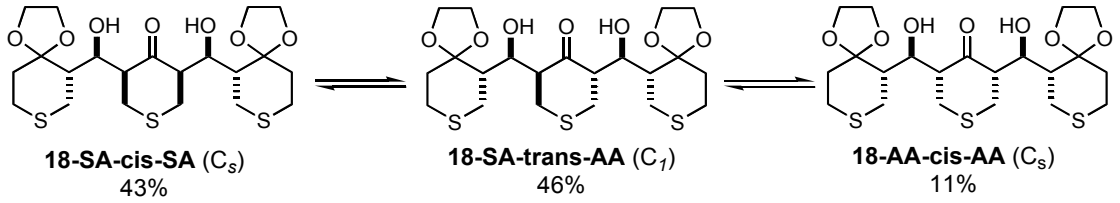


Figure 25. Isomerization of **18-SA-trans-AA** with 0.3 M imidazole in $CDCl_3$.

2.6.9. Bis-aldol 18-AS-TES-trans-SA

The adduct **18-AS-TES-trans-SA** was obtained as the minor product from the aldol reaction of **17-AS-TES** with **15** (Figure 26). Removal of the triethylsilyl protecting group under HF·pyridine/pyridine conditions gave **18-AS-trans-SA** (=**18-SA-trans-AS**) (quantitative yield) whose structure determination has been previously described.[11]

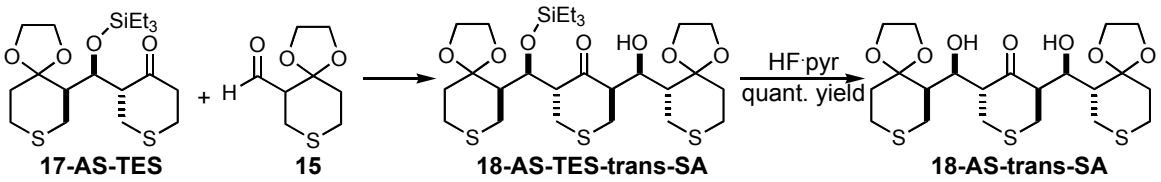


Figure 26. Determination of the relative configuration of **18-AS-TES-trans-SA**.

2.6.10. Bis-aldol 18-AS-TES-trans-AA

The adduct **18-AS-TES-trans-AA** was obtained as the major product from the aldol reaction of **17-AS-TES** with **15** (Figure 27). Removal of the triethylsilyl protecting group under HF·pyridine/pyridine conditions gave **18-AS-trans-AA** (=**18-AA-trans-AS**) (quantitative yield) whose structure determination has been previously described.[11]

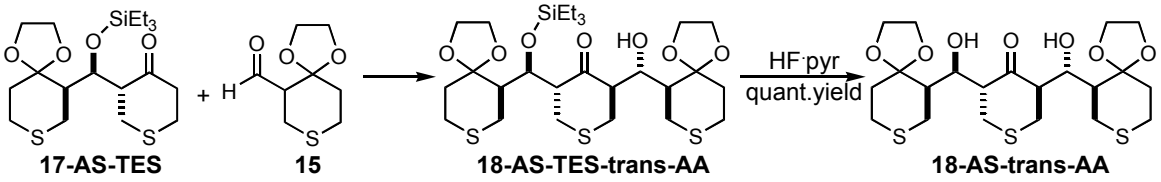


Figure 27. Determination of the relative configuration of **18-AS-TES-trans-AA**.

2.6.11. Bis-aldol 18-SS-TES-trans-SA

The adduct **18-SS-TES-trans-SA** was obtained from the aldol reaction of **17-SS-TES** with **15** (Figure 28). Removal of the triethylsilyl protecting group under HF·pyridine/pyridine conditions gave **18-SS-trans-SA** (=**18-SA-trans-SS**) (quantitative yield) whose structure determination has been previously described.[11]

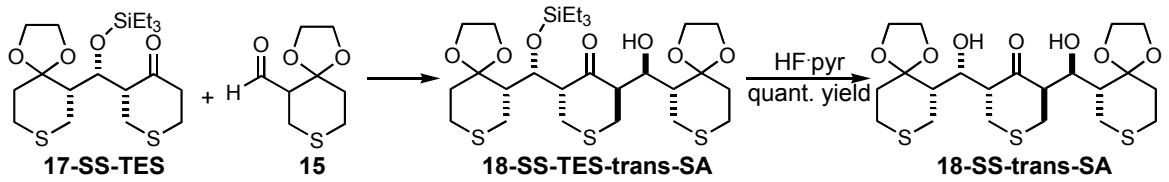


Figure 28. Determination of the relative configuration of **18-SS-TES-trans-SA**.

2.6.12. Bis-aldol 18-SS-TES-trans-AA

The adduct **18-SS-TES-trans-AA** was obtained from the aldol reaction of **17-SS-TES** with **15** (Figure 29). Removal of the triethylsilyl protecting group under HF·pyridine/pyridine conditions gave **18-SS-trans-AA** (=**18-AA-trans-SS**) (quantitative yield) whose structure determination has been previously described.[11]

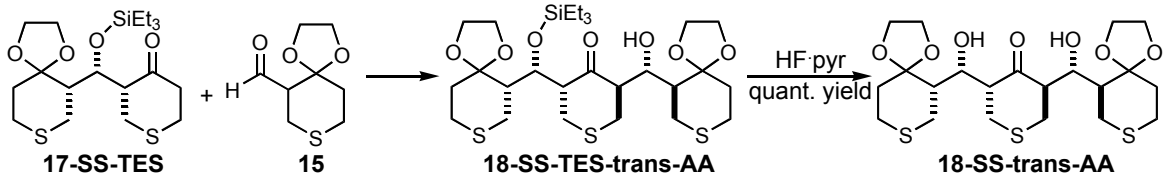


Figure 29. Determination of the relative configuration of **18-SS-TES-trans-AA**.

2.6.13. Bis-aldol 18-SA-cis-SA

The isomerization of **18-SA-trans-AA** (=**18-AA-trans-SA**) in 0.3 M imidazole in $CDCl_3$ gave an equilibrium mixture in 2-3 days with the **18-SA-trans-AA** diastereomer predominating (46%), and two C_s compounds: **18-SA-cis-SA** (43%) and **18-AA-cis-AA** (11%) (Figure 25). At present, this is the only route to these adducts. **18-SA-cis-SA** is symmetrical as indicated by the presence of only 11 resonances in the ^{13}C NMR spectrum. The structure of **18-SA-cis-SA** is assigned based on the chemical shift of 70.8 ppm for C-1'/1'' in the ^{13}C NMR spectrum; this result is consistent with the syn-anti relative configuration (7 examples).

2.6.14. Bis-aldol 18-AA-cis-AA

The isomerization of **18-SA-trans-AA** (=**18-AA-trans-SA**) in 0.3 M imidazole in $CDCl_3$ gave an equilibrium mixture in 2-3 days with the **18-SA-trans-AA** diastereomer predominating (46%), and two C_s compounds: **18-SA-cis-SA** (43%) and **18-AA-cis-AA** (11%) (Figure 25). **18-AA-cis-AA**

is symmetrical as indicated by the presence of only 11 resonances in the ^{13}C NMR spectrum. The structure of **18-AA-cis-AA** is assigned based on the chemical shift of 72.4 ppm for C-1'/1'' in the ^{13}C NMR spectrum; this result is consistent with the anti-anti relative configuration (7 examples).

2.6.15. Bis-aldol 18-SA-cis-AA (=18-AA-cis-SA)

The isomerization of **18-AA-trans-AA** in CH_2Cl_2 with imidazole for 3 days at room temperature gave a mixture of **18-SA-cis-AA** (46%), **18-SA-trans-SA** (29%) and **18-AA-trans-AA** (25%) (Figure 21). The equilibrium ratio was confirmed by isomerising **18-SA-trans-SA** in 0.3 M imidazole in $CDCl_3$ was prepared and monitoring by ^1H NMR. A comparable equilibrium mixture of **18-SA-cis-AA** (47%), **18-SA-trans-SA** (26%) and **18-AA-trans-AA** (26%) was obtained after 11 days (Figure 18). **18-SA-cis-AA** (=**18-AA-cis-SA**) is unsymmetrical as indicated by the presence of 21 resonances in the ^{13}C NMR spectrum. The structure of **18-SA-cis-AA** (=**18-AA-cis-SA**) is established because it is the only possible bis-aldol adduct that can be obtained from the imidazole-catalyzed isomerizations of **18-AA-trans-AA** and **18-SA-trans-SA**.

3. CONCLUSION

The initial goal of this project was to access the enantioenriched non-Felkin (C1'-C6'' anti) diastereomers of the first aldol reaction. This would necessitate controlling both the diastereo- and enantioselectivity during the reaction of **15** with **16** and it must be achieved in good yield. The challenge is to overcome the inherent preference for Felkin addition to aldehyde **15**. Conditions for the first aldol reaction have been explored using chiral transition metal-based Lewis acids and organocatalysts with chelating Lewis acid additives to access non-racemic non-Felkin first aldol adducts. Despite extensive experimentation, the direct synthesis of non-racemic **17-AA** and **17-SA** remains elusive at this time.

The soft enolization methodology was applied to the first and second aldol reactions of the TR2P. The method developed for the synthesis of **17-AA** was shown to be comparable in yield to the previously reported Mukaiyama-type aldol reaction; the Mukaiyama aldol reaction is superior for access to the **17-SA** diastereomer. The soft enolization methodology was successfully applied to the formation of the non-Felkin bis-aldol diastereomers **18**. Three of the previously six unknown diastereomers are available selectively via this new route. Although the yields were moderate, the reaction was highly stereoselective, cleanly producing only two of eight possible diastereomers for reactions with **17-SA-TES**, **17-AA-TES**, **17-SA-MOM, 17-AS-TES** and **17-SS-TES**. The yields will need to be improved for future synthetic applications of these adducts; however, single adducts might be available by using enantiopure reactants. Although the *cis*-substituted bis-aldol adducts (**18-SA-cis-SA**, **18-SA-cis-AA**, and **18-AA-cis-AA**) are not available directly, they can be obtained through isomerization. Thus, all of the 20 bis-aldol diastereomers of the TR2P are now known and can be obtained via sequential aldol reactions of **15** with **16** in 2-5 steps.

3.1. Future Directions

The soft enolization methodology gave access to non-Felkin first-aldol diastereomers and 3 previously unknown bis-aldol diastereomers; however, an improved method will be required to access synthetically useful amounts of these materials. Pre-forming the magnesium

(II) enolate (e.g., prepared from X-Mg-NR base) and reacting with aldehyde **15** pre-complexed with $MgBr_2 \cdot OEt_2$ could potentially maintain the non-Felkin diastereoselectivity while improving the yield of the first and second aldol reactions.[27]

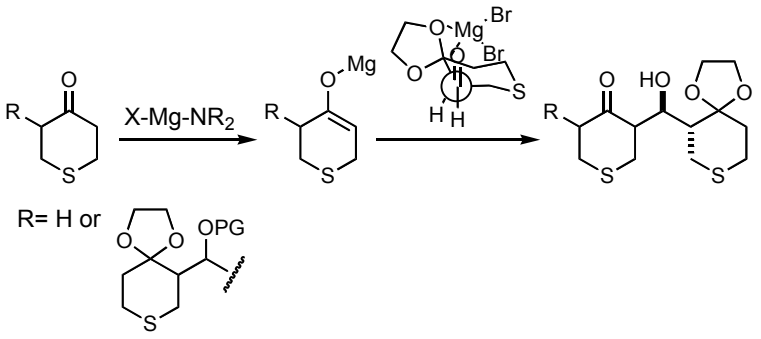


Figure 30. Pre-forming the magnesium (II) enolate.

4. EXPERIMENTAL

4.1. GENERAL METHODS

Anhydrous solvents were distilled under an argon atmosphere as follows: tetrahydrofuran (THF) from benzophenone sodium ketyl; CH_2Cl_2 from CaH_2; MeOH from $Mg(OMe)_2$. All experiments involving air- and and/or moisture-sensitive compounds were conducted in an oven-dried round-bottom flask capped with a rubber septum, and attached via a needle and connecting tubing to an argon manifold equipped with mercury bubbler (ca. 5 mm positive pressure of argon). Low temperature baths were: ice/water (0 ^{o}C), $CO_{2(s)}$/water/ice (-20 ^{o}C), and $CO_{2(s)}$/acetone (-78 ^{o}C). Unless otherwise noted, reaction temperatures refer to that of the bath.

Concentration refers to removal of volatiles at water aspirator pressure on a rotary evaporator. Preparative TLC (PTLC) was carried out on glass plates (20x20 cm) pre-coated (0.25 mm) with silica get 60 F_{254}. Materials were detected by visualization under an ultraviolet lamp (254 nm) and/or by treating a 1 cm vertical strip removed from the plate with a solution of phophomolybdic acid (5%) containing traces of ceric sulfate in aqueous sulfuric acid (5% v/v) followed by charring on a hot plate. Flash column chromatography (FCC) was performed according to Still et al. with silica gel 60 (40-63 μm).[28] All mixed solvent eluents are reported as v/v solutions. Unless otherwise noted, all reported compounds were homogeneous by thin layer chromatography (TLC) and by ^{1}H NMR.

4.2. SPECTRAL DATA

High resolution mass spectra (HRMS) and low resolution mass spectra (LRMS) were obtained on a double focusing high resolution spectrometer; only partial data are reported. EI ionization was accomplished at 70 eV and CI ionization at 50 eV with ammonia as the reagent gas; only a partial data are reported. IR spectra were recorded on a Fourier transform interferometer using a diffuse reflectrance cell (DRIFT); only diagnostic and/or intense peaks are reported. NMR spectra were measured in $CDCl_3$ solution at 500 MHz or 600 MHz for ^{1}H and

125 MHz or 150 MHz for ^{13}C. Signals due to the solvent (^{13}C NMR) or residual protonated solvent (^{1}H NMR) served as the internal standard: $CDCl_3$ (7.26 δ_H, 77.23 δ_C). The ^{1}H NMR chemical shifts and coupling constants were determined assuming first-order behaviour. Multiplicity is indicated by one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br (broad), ap (apparent); the list of coupling constants (*J*) corresponds to the order of the multiplicity assignment. Coupling constants (*J*) are reported to the nearest 0.5 Hz (digital resolution ca. 0.2 Hz/pt). The ^{1}H NMR assignments were made based on chemical shift and multiplicity and were confirmed, where necessary, by homonuclear decoupling and/or two-dimensional correlation experiments (gCOSY, gHSQC, gHMBC).[29] The ^{13}C NMR assignments were made on the basis of chemical shift and multiplicity (as determined by 13C-DEPT or gHSQC) and were confirmed, where necessary, by two-dimensional $^{1}H/^{13}C$ correlation experiments (gHSQC and/or g HMBC).[4, 29]

4.3. MATERIALS

The preparations of the following compounds have been previously described: **179**;[26] **48**;[30] **15**;[6] **16**, **17-SS**, **17-AS**, **17-SA**;[7] **17-AA**;[9] **17-SA-TES**, **17-SA-MOM**, **17-AA-TES**, **17-AA-MOM**, **17-AS-TES**, **17-SS-TES;**[10] $^{i}Pr_2NEt$ was distilled from KOH under argon and was stored over KOH. $CDCl_3$ was treated with basic Al_2O_3 before use. All other reagents were commercially available and unless otherwise noted, were used as received.

4.4. GENERAL EXPERIMENTAL PROCEDURES

4.4.1. General Procedure for Aldol Reactions of 16 with 15 via Soft Enolization

$MgBr_2 \cdot OEt_2$ (6 equiv) was added to a stirred solution of aldehyde **15** (1 equiv, 0.03 M in CH_2Cl_2) at room temperature under Ar. After 10 min, ketone **16** (1 equiv) was added and the reaction was cooled to 0 °C over 10 min. *i*-Pr_2NEt (1 equiv) was added dropwise and the reaction mixture was allowed to stir at 0 °C for 10 min and was quenched by the addition of

[4] The multiplicity of the ^{13}C NMR signals refers to the number of attached H's (i.e., s = C, d = CH_2, q = CH_3)

water with vigorous stirring. The mixture was diluted with ethyl acetate and transferred to a separatory funnel containing saturated Na_2CO_3 solution with ethyl acetate. The organic layer was removed and the aqueous layer was washed with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude products. By addition of a carefully measured amount of 1,4-dicyanobenzene, the combined yield of **17** was determined.

4.4.2. Procedure for Aldol Reactions of 16 with 15 via Soft Enolization on 0.5-mmol scale

$MgBr_2 \cdot OEt_2$ (6 equiv, 798 mg) was added to a stirred solution of aldehyde **15** (97 mg, 0.52 mmol, 0.03 M in CH_2Cl_2) at room temperature under Ar. After 10 min, ketone **16** (2 equiv, 121 mg, 1.0 mmol) was added and the reaction was cooled to 0 °C over 15 min. *i*-Pr_2NEt (1 equiv) was added dropwise over 10 seconds. The reaction mixture was allowed to stir at 0 °C for 10 min and then was quenched by addition of 50 mL of ice-cold phosphate buffer (pH 7). The mixture was allowed to warm to room temperature with vigorous stirring and was transferred to a separatory funnel with CH_2Cl_2. If the organic layer was not clear, brine was added. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to provide the crude products. Analysis by ^1H NMR revealed a 39:61:1:0 mixture of **17-AA**, **17-SA**, **17-AS** and **17-SS**, respectively in addition to **15**. By addition of a carefully measured amount of 1,4-dicyanobenzene, the combined yield of **17** was determined to be 65%. 2-5 mL of methanol were added to the crude mixture and 69 mg (44%) of insoluble **17-SA** was filtered off. The mother liquor was concentrated to give 155 mg of 78:22 **17-AA** and **17-AS** in addition to some bis-aldols **18** and **15** (**17-SA** not detected). Fractionation of the crude by FCC (30% ethyl acetate/hexanes to 100% ethyl acetate) gave a 81:18:2 mixture of **17-AA**, **17-SA** and **17-AS**, respectively (43 mg, 27%) and 13 mg of bis-aldols **18** (10% based on **15**).

4.4.3. General Procedure for Aldol Reactions of 17 with 15 via Soft Enolization

$MgBr_2 \cdot OEt_2$ (6 equiv) was added to a stirred solution of aldehyde **15** (1 equiv, 0.03 M in CH_2Cl_2) at room temperature under Ar. After 10 min, the reaction was cooled to 0 ^oC and the ketone **17** (1 equiv) and *i*-Pr_2NEt (1 equiv) were sequentially added. The reaction mixture was allowed to stir for 10-30 min and then was quenched by addition of ice-cold phosphate buffer

(pH 7). The mixture was allowed to warm to room temperature with vigorous stirring and was transferred to a separatory funnel with CH_2Cl_2. If the organic layer was not clear, brine was added. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to provide the crude products. Analysis by ^1H NMR revealed a mixture of two aldol adducts in addition to **15** and **17**; other adducts, if present, were not detected.

4.4.4. General Procedure for TES deprotection

A 6 M solution of HF·pyridine was prepared by adding commercial HF·pyridine (70% HF, 30% pyridine; 0.19 mL) and pyridine (0.57 mL) to THF (1.0 mL). The above solution was added to the TES-containing substrate and the resulting solution was stirred at room temperature until the reaction was complete by TLC analysis (4 to 48 h). The mixture was diluted with a 3:1 mixture of hexane and CH_2Cl_2 (v/v), respectively, washed sequentially with saturated aqueous $NaHCO_3$ and 2% citric acid solution, dried over Na_2SO_4, and concentrated to give the crude product.

4.4.5. General Procedure for MOM deprotection

The following procedure was used without optimization for conversion. $TiCl_4$ (5 equiv) was added dropwise over 10 seconds to a stirred solution of substrate in CH_2Cl_2 (50 mL/ mmol) at -78 ^oC under argon. After 5 minutes, a fine yellow slurry developed. Thiophenol (10 equiv) was added dropwise over 10 seconds and the resultant red-orange fine slurry was stirred for a further 10 minutes at -78 ^oC. MeOH (0.5 mL) was added and the cooling bath bath was removed (reaction became colourless upon addition of MeOH). The solution was stirred vigorously for 1 minute followed by the addition of phosphate buffer (3 mL, pH 7). After 3 minutes, the mixture was diluted with saturated Na_2CO_3 and extracted with CH_2Cl_2 (3x). The combined organic extracts were dried over Na_2SO_4 and concentrated to give the crude product.

4.4.6. General Procedure for Reduction with $NaBH_4$[7]

$NaBH_4$ (2 equiv) was added to a stirred solution of the ketone in ethanol (0.1 M) at rt. After 1 h, the reaction was quenched by dropwise addition of aqueous HCl (1 M) until gas evolution ceased. The mixture was neutralized by addition of 15% aqueous NaOH and, after 30

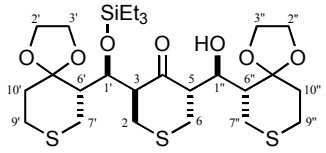
min, was extracted with ethyl acetate (x3). The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude product.

4.4.7. General Procedure for Isomerization[8]

The bis-aldol substrate was dissolved in solution of imidazole in CH_2Cl_2 (0.8 M; ca. 1 mL/10 mg substrate) and the resulting solution allowed to stand at room temperature. After sufficient time to reach equilibrium, the mixture was diluted with citric acid (0.1 M) and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude products.

4.5. EXPERIMENTAL PROCEDURES AND SPECTRAL DATA FOR COMPOUNDS

(3*S*,5*S*)-*rel*-3-[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*R*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-SA-TES-trans-AA)



Following the above General Procedure, reaction of **17-SA-TES** (215 mg, 0.514 mmol) with **15** (101 mg, 0.538 mmol) for 60 min gave a crude that contained a 25:36:26:13 mixture of **15**, **17-SA-TES**, **18-SA-TES-trans-AA**, and **18-SA-TES-trans-SA**, respectively. Fractionation of the crude by FCC (30% ethyl acetate/hexanes) gave **18-SA-TES-trans-AA** (23 mg, 7%), and a 2:1 mixture of **18-SA-TES-trans-AA** and **18-SA-TES-trans-AA**, respectively (109 mg, 35%). A concentrated (15mg/1mL) solution of **18-SA-TES-trans-AA** in acetonitrile when stored in a refrigerator (ca. 5 °C) deposited crystals suitable for XRD analysis (see Appendix A for X-ray data).

IR ν_{max} 3484, 1707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.09 (1H, d, *J* = 2.5 Hz, HC-1'), 4.37 (1H, ddd, *J* = 3.5, 5, 7 Hz, HC-1"), 4.04-3.88 (6H, m, HCO ×6), 3.74 (1H, d, *J* = 3.5 Hz, HO), 3.80-3.67 (2H, m, HCO ×2), 3.46 (1H, dd, *J* = 8, 8.5 Hz, HC-3), 3.21 (1H, dd, *J* = 8, 13.5 Hz, HC-6), 3.05-2.82 (8H, m, H_2C-

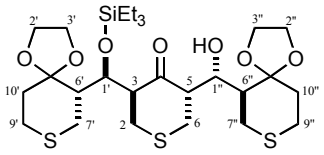
2, HC-5, H_2C-7', H_2C-7", HC-9'), 2.79 (1H, dd, *J* = 4, 13.5 Hz, HC-6), 2.75-2.63 (2H, m, HC-9"), 2.45 (1H, br d, *J* = 13.5 Hz, HC-9'), 2.26-2.18 (2H, m, HC-6', HC-6"), 2.18-2.11 (1H, m, HC-10"), 2.01 (1H, ddd, *J* = 3, 3, 13.5 Hz, HC-10'), 1.80-1.73 (1H, m, HC-10"), 1.69 (1H, ddd, *J* = 3.5, 13, 13.5 Hz, HC-10'), 0.93 (9H, t, *J* = 8 Hz, H_3C ×3), 0.66-0.59 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0 (s, C-4), 111.1 (s, C-5"), 108.8 (s, C-5'), 73.9 (s, C-1"), 65.0 (t, CH_2O), 64.6 (d, C-1'), 64.5 (t, CH_2O), 64.2 (t, CH_2O), 64.0 (t, CH_2O), 54.7 (d, C-5 or C-6'), 54.6 (d, C-5 or C-6'), 52.1 (d, C-3), 46.0 (d, C-6"), 37.7 (t, C-10'), 34.9 (t, C-10"), 30.6 (t, C-7"), 30.0 (t, C-6), 27.71 (t, C-2 or C-7'), 27.68 (t, C-2 or C-7'), 27.1 (t, C-9'), 26.8 (t, C-9"), 7.2 (q ×3, CH_3), 5.2 (t ×3, CH_2Si).

LRMS (EI), *m/z* (relative intensity): 606 ($[M]^+$, 0.1), 577 (1), 559 (1), 389 (12), 245 (30), 229 (36), 171 (27), 132 (41), 99 (100).

HRMS *m/z* calcd for $C_{27}H_{46}O_7S_3Si$ 606.2175, found 606.2178 (EI).

(3*S*,5*S*)-*rel*-3-[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-SA-TES-trans-SA)



From aldol reaction of **17-SA-TES** with **15**. See experimental procedure for compound **18-SA-TES-trans-AA**.

IR ν_{max} 3482, 1711 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.16 (1H, d, *J* = 2.5 Hz, HC-1'), 4.65 (1H, br d, *J* = 9 Hz, HC-1"), 4.06-3.90 (6H, m, H_2CO ×6), 3.83 (1H, s, HO), 3.82-3.68 (2H, m, HCO ×2), 3.41 (1H, dd, *J* = 7, 10 Hz, HC-3), 3.35 (1H, dd, *J* = 12, 13.5 Hz, HC-6), 3.05 (1H, dd, *J* = 7, 12.5 Hz, HC-2), 2.98 (1H, dd, *J* = 12, 12.5 Hz, HC-2), 2.95-2.81 (3H, m, H_2C-7', HC-9'), 2.81-2.70 (3H, m, HC-7", H_2C-9"), 2.67 (1H, br dd, *J* = 5, 12 Hz, HC-5), 2.57 (1H, dd, *J* = 7.5, 14 Hz, HC-7"), 2.51 (1H, dd, *J* = 5, 13.5 Hz, HC-6), 2.46 (1H, br dd, *J* = 2, 13.5 Hz, HC-9'), 2.20 (2H, m, HC-10", HC-7'), 2.01 (1H, br d, *J* = 13.5 Hz, HC-10'), 1.93 (1H, ddd, *J* = 3, 7.5, 9 Hz, HC-6"), 1.83-1.78 (1H, m,

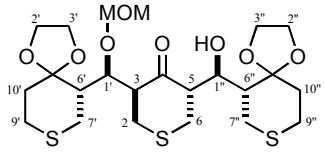
HC-10''), 1.70 (1H, ddd, J = 3, 13, 13.5 Hz, HC-10'), 0.93 (9H, t, J = 8 Hz, H_3C ×3), 0.62 (6H, ap q, J = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.9 (s, C-4), 110.8 (s, C-5''), 108.8 (s, C-5'), 71.7 (d, CH-1''), 65.0 (t, CH_2O), 64.9 (t, CH_2O), 64.8 (d, C-1'), 64.3 (t, CH_2O), 64.2 (t, CH_2O), 54.5 (d, C-6'), 53.5 (d, CH-5), 51.4 (d, C-3), 46.7 (d, C-6''), 37.8 (t, C-10'), 34.6 (t, C-10''), 29.1 (t, C-7''), 27.6 (t, C-7'), 27.1 (t, C-9'), 26.8 (t, C-9''), 23.8 (t, C-2), 22.1 (t, C-6), 7.1 (q ×3, CH_3), 5.20 (t ×3, CH_2Si).

LRMS (EI), *m/z* (relative intensity): 606 ($[M]^+$, 0.1), 559 (1), 474 (3.3), 389 (13), 229 (37), 171 (29), 99 (100).

HRMS *m/z* calcd for $C_{27}H_{46}O_7S_3Si$ 606.2175, found 606.2153 (EI).

(3*S*,5*S*)-*rel*-3-[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*R*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-SA-MOM-trans-AA)



The ketone **17-SA-MOM** (19 mg, 0.055 mmol) was added to a stirred suspension of *i*-Pr_2NEt (9 uL, 0.06 mmol), $MgBr_2{\cdot}OEt_2$ (82 mg, 0.32 mmol) and **1** (10 mg, 0.053 mmol) in CH_2Cl_2 (1.8 mL). After 60 min, the reaction was quenched and worked up as described in the General Procedure to give a crude that contained a 27:40:22:11 mixture of **15**, **17-SA-MOM**, **18-SA-MOM-trans-AA**, and **18-SA-MOM-trans-SA**, respectively; by addition of a carefully measured amount of 1,4-dicyanobenzene, the combined yield of bis-aldol adducts was determined to be 25%. The crude products from several similar experiments were combined and fractionated by PTLC (5% ethyl acetate, 15% acetone in hexanes, several elutions) to provide pure samples of **18-SA-MOM-trans-AA** and **18-SA-MOM-trans-SA**. A saturated solution of **18-SA-MOM-trans-SA** in acetonitrile when stored in a refrigerator (ca. 5°C) deposited crystals suitable for XRD analysis (see Appendix B for X-ray data).

IR ν_{max} 3483, 1707 cm^{-1}.

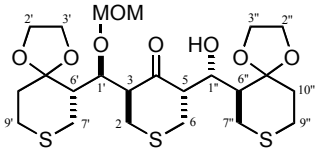
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (1H, d, *J* = 6.5 Hz, HCO_2), 4.79 (1H, br s, HC-1'), 4.64 (1H, d, *J* = 6.5 Hz, HCO_2), 4.36 (1H, ddd, *J* = 3, 4.5, 7 Hz, HC-1"), 4.02-3.96 (6H, m, H_2CO ×3), 3.86 (1H, d, *J* = 3 Hz, HO), 3.81-3.73 (2H, m, H_2CO), 3.54 (1H, ddd, *J* = 1.5, 6.5, 10.5 Hz, HC-3), 3.36 (3H, s, H_3CO), 3.26 (1H, dd, *J* = 9, 13.5 Hz, HC-6), 3.11 (1H, dd, *J* = 7, 13.5 Hz, HC-2), 3.00-2.79 (7H, m, HC-5, H_2C-7', H_2C-7", HC-9', HC-2), 2.79 (1H, dd, *J* = 5, 13.5 Hz, HC-6), 2.77-2.62 (2H, m, H_2C-9"), 2.52-2.44 (2H, m, HC-6', HC-9'), 2.22 (1H, ddd, *J* = 3.5, 7, 7.5 Hz, HC-6"), 2.14 (1H, ddd, *J* = 3, 8.5, 13.5 Hz, HC-10"), 2.04 (1H, ddd, *J* = 3, 3.5, 13.5 Hz, HC-10'), 1.77 (1H, ddd, *J* = 3.5, 7.5, 13.5 Hz, HC-10"), 1.72 (1H, ddd, *J* = 3.5, 13, 13.5 Hz, HC-10').

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.0 (s, C-4), 111.0 (s, C-5"), 108.8 (s, C-5'), 97.8 (t, OCH_2O), 73.7 (d, C-1"), 72.2 (d, CH-1'), 64.9 (t, CH_2O), 64.6 (t, CH_2O), 64.1 (t, CH_2O), 64.0 (t, CH_2O), 56.2 (d, CH_3O), 54.3 (d, C-5), 52 (d, C-3), 51.6 (d, C-6'), 45.9 (d, C-6"), 37.3 (t, C-10'), 34.6 (t, C-10"), 30.3 (t, C-7"), 29.6 (t, C-6), 28.5 (t, C-7'), 27.3 (t, C-2), 27.1 (t, C-9'), 26.8 (t, C-9").

LRMS (EI), *m/z* (relative intensity): 536 ($[M]^+$, 0.1), 474 (7), 412 (7), 286 (11), 224 (9), 188 (13), 159 (17), 133 (73), 99 (100).

HRMS *m/z* calcd for $C_{23}H_{36}O_8S_3$ 536.1565, found 536.1567 (EI).

(3*S*,5*S*)-*rel*-3-[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(methoxymethoxy)methyl]-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-SA-MOM-trans-SA)



From aldol reaction of **17-SA-MOM** with **15**. See experimental procedure for compound **18-SA-MOM-trans-AA**.

IR ν_{max} 3482, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.86 (1H, br s, HC-1'), 4.79 (1H, d, *J* = 6.5 Hz, HCO_2), 4.64 (1H, br d, *J* = 3 Hz, HC-1"), 4.63 (1H, d, *J* = 6.5 Hz, HCO_2), 4.12-3.76 (8H, m, H_2CO ×4), 3.83 (1H, br s, HO), 3.46 (1H, dd, *J* = 7, 9.5 Hz, HC-3), 3.35 (3H, s, H_3CO), 3.35 (1H, dd, *J* = 11.5, 13.5 Hz, HC-6), 3.11 (1H, dd, *J* = 7, 12.5 Hz, HC-2), 2.97 (1H, dd, *J* = 10, 12.5 Hz, HC-2), 2.95-2.68

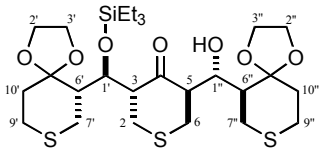
(7H, m, HC-5, H_2C-7', HC-7", H_2C-9', HC-9"), 2.57 (1H, dd, *J* = 7.5, 14 Hz, HC-7"), 2.54 (1H, dd, *J* = 5.5, 13.5 Hz, HC-6), 2.51-2.42 (2H, m, HC-6', HC-9'), 2.20-2.14 (1H, m, HC-10"), 2.03 (1H, ddd, *J* = 3, 3.5, 13.5 Hz, HC-10'), 1.93 (1H, ddd, *J* = 3, 7.5, 8.5 Hz, HC-6"), 1.83-1.76 (1H, m, HC-10"), 1.72 (1H, ddd, *J* = 3.5, 13, 13.5 Hz, HC-10').

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.3 (s, C-4), 110.7 (s, C-5"), 108.8 (s, C-5'), 97.8 (t, OCH_2O), 72.2 (d, C-1'), 72.0 (d, C-1"), 64.95 (t, CH_2O), 64.92 (t, CH_2O), 64.26 (t, CH_2O), 64.22 (t, CH_2O), 56.2 (q, CH_3O), 53.5 (d, C-5), 51.4 (d, C-6'), 51.2 (d, C-3), 46.5 (d, C-6"), 37.5 (t, C-10'), 34.5 (t, C-10"), 29.2 (t, C-7"), 28.3 (t, C-7'), 27.1 (t, C-9'), 26.8 (t, C-9"), 24.3 (t, C-2), 22.4 (t, C-6).

LRMS (EI), *m/z* (relative intensity): 518 ([M-18]$^+$, 0.1), 348 (1), 286 (9), 188 (9), 159 (9), 132 (50), 99 (100), 86 (19), 54 (22).

HRMS *m/z* calcd for $C_{23}H_{36}O_8S_3$ 536.1572 (537.1651 for M+H), found 537.1662 (CI, NH_3).

(3*R*,5*R*)-*rel*-3-[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-AA-TES-trans-AA)



Following the above General Procedure, reaction of **17-AA-TES** (199 mg, 0.476 mmol) with **15** (92 mg, 0.49 mmol) for 60 min gave a crude that contained a 27:21:19:32 mixture of **15**, **17-AA-TES**, **18-AA-TES-trans-AA**, and **4-AA-TES-trans-SA**, respectively. Fractionation of the crude by FCC (30% ethyl acetate/hexanes) gave **18-AA-TES-trans-AA** (46 mg, 16%), **18-AA-TES-trans-SA** (85 mg, 30%).

IR ν_{max} 3505, 1702 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.52 (1H, dd, *J* = 2.5, 4 Hz, HC-1'), 4.16 (1H, ddd, *J* = 3.5, 4, 7 Hz, HC-1"), 4.11-3.88 (8H, m, H_2CO ×4), 3.88 (1H, d, *J* = 4 Hz, HO), 3.22 (1H, dd, *J* = 11, 13 Hz, HC-6), 3.21 (1H, ddd, *J* = 4, 4.5, 5.5 Hz, HC-3), 3.03 (1H, dd, *J* = 12, 13.5 Hz, HC-7'), 2.97-2.78 (7H, m, H_2C-2, HC-5, HC-6, HC-7", HC-9', HC-9"), 2.73-2.61 (2H, m, HC-7', CH-9"), 2.58

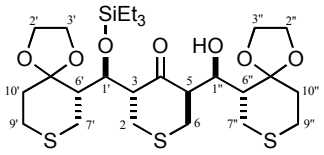
(1H, dd, *J* = 7, 14 Hz, HC-7''), 2.51-2.43 (2H, m, HC-6'', HC-9'), 2.26 (1H, ddd, *J* = 2.5, 3, 12 Hz, HC-6'), 2.16 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-10''), 2.11 (1H, br d, *J* = 13.5 Hz, HC-10'), 1.79 (1H, ddd, *J* = 3.5, 7, 13.5 Hz, HC-10''), 1.66 (1H, ddd, *J* = 4, 13, 13.5 Hz, HC-10'), 0.97 (9H, t, *J* = 8 Hz, H_3C ×3), 0.67 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 209.8 (s, C-4), 110.5 (s, C-5''), 108.9 (s, C-5'), 72.81 (d, C-1' or C-1''), 72.77 (d, C-1' or C-1''), 64.9 (t, CH_2O), 64.3 (t, CH_2O), 64.2 (t, CH_2O), 64.1 (t, CH_2O), 53.9 (d, C-3), 53.8 (d, C-6'), 53.5 (d, C-5), 46.1 (d, C-6''), 37.0 (t, C-10'), 34.5 (t, C-10''), 33.6 (t, C-2), 32.1 (t, C-6), 30.3 (t, C-7''), 27.9 (t, C-7'), 26.95 (t, C-9' or C-9''), 26.91 (t, C-9' or C-9''), 7.3 (q ×3, CH_3), 5.5 (t ×3, CH_2Si).

LRMS (CI, NH_3), *m/z* (relative intensity): 607 ($[M+1]^+$, 1), 419 (100), 287 (90), 229 (34), 225 (23), 189 (92), 132 (35), 99 (44).

HRMS *m/z* calcd for $C_{27}H_{46}O_7S_3Si$ 606.2175 (607.2253 for M+H), found 607.2260 (CI, NH_3).

(3*R*,5*R*)-*rel*-3-[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*R*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-AA-TES-trans-SA)



From aldol reaction of **17-AA-TES** with **15**. See experimental procedure for compound **18-AA-TES-trans-AA**.

IR ν_{max} 3501, 1707 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65-4.63 (2H, m, HC-1', HC-1''), 4.09-3.84 (8H, m, H_2CO ×4), 3.83 (1H, s, HO), 3.26-3.20 (1H, m, HC-6), 3.18 (1H, ddd, *J* = 5, 5, 5 Hz, HC-3), 3.00 (1H, dd, *J* = 5, 13.5 Hz, HC-2), 2.98 (1H, dd, *J* = 12, 14 Hz, HC-7''), 2.87-2.55 (10H, m, HC-2, HC-5, HC-6, H_2C-7', H_2C-7'', HC-9', H_2C-9''), 2.47 (1H, br d, *J* = 13.5 Hz, HC-9'), 2.27 (1H, ddd, *J* = 2, 3, 9 Hz, HC-6'), 2.17 (1H, ddd, *J* = 3, 7, 13.5 Hz, HC-10''), 2.11 (1H, ddd, *J* = 3, 3.5, 13.5 Hz, HC-10'), 2.00 (1H, ddd, *J* = 3, 8.5, 9 Hz, HC-6''), 1.81 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-10''), 1.67

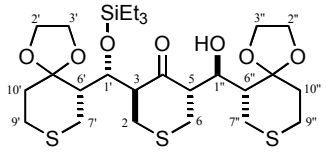
(1H, ddd, J = 3.5, 13, 13.5 Hz, HC-10'), 0.96 (9H, t, J = 8 Hz, H_3C ×3), 0.72-0.58 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.1 (s, C-4), 110.7 (s, C-5''), 108.9 (s, C-5''), 71.9 (d, C-1'), 68.6 (d, C-1''), 65.0 (t, CH_2O), 64.30 (t, CH_2O), 64.29 (t, CH_2O), 4.0 (t, CH_2O), 53.7 (d, C-6'), 53.5 (d, C-3), 52.9 (d, C-5), 47.6 (d, C-6''), 37.1 (t, C-10'), 35.5 (t, C-10''), 32.6 (t, C-2), 29.1 (t, C-7''), 28.0 (t, C-7'), 27.5 (t, C-6), 26.9 (t, C-9'), 26.8 (t, C-9''), 7.2 (q ×3, CH_3), 5.6 (t ×3, CH_2Si).

LRMS (CI, NH_3), *m/z* (relative intensity): 607 ($[M+1]^+$, 5), 475 (13), 419 (80), 389 (17), 287 (95), 229 (44), 189 (100), 99 (71).

HRMS *m/z* calcd for $C_{27}H_{46}O_7S_3Si$ 606.2175 (607.2253 for M+H), found 607.2244 (CI, NH_3).

(3*S*,5*S*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*R*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-AS-TES-trans-AA)



Following the above General Procedure, reaction of **17-AS-TES** (120 mg, 0.287 mmol) with **15** (60 mg, 0.32 mmol) for 15 min gave a crude that contained a 20:18:32:29 mixture of **15**, **17-AS-TES**, **18-SS-TES-trans-AA**, and **18-SS-TES-trans-SA**, respectively. Fractionation of the crude by FCC (30% Ethyl acetate/hexanes) gave **17-AS-TES** (35 mg, 29%), and a 1:1.5 mixture (114 mg, 66%) of **18-AS-TES-trans-AA** and **18-AS-TES-trans-SA**, respectively. The bis-aldol mixture (56 mg) was further fractionated by PTLC (30% ethyl acetate/hexanes, multiple elutions) to give **18-AS-TES-trans-AA** (34 mg) and **18-AS-TES-trans-AA** (20 mg).

IR ν_{max} 3493, 1716 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (1H, br s, HC-1'), 4.21 (1H, ddd, J = 3, 3, 8 Hz, HC-1''), 4.01-3.84 (9H, m, HO, H_2CO ×4), 3.19 (1H, dd, J = 11.5, 14 Hz, HC-6), 3.13 (1H, dd, J = 11, 12 Hz, HC-2), 2.94-2.74 (8H, m, HC-2, HC-3, HC-5, HC-6, HC-7', H_2C-7'', HC-9'), 2.70-2.58 (4H, m, HC-7', H_2C-9', HC-9''), 2.50 (1H, ddd, J = 3, 7, 7.5 Hz, CH-6''), 2.18-2.07 (3H, m, CH-6',

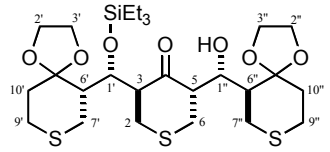
CH-10', CH-10''), 1.82 (1H, ddd, *J* = 3, 7, 13.5 Hz, CH-10'), 1.56 (1H, ap ddd, *J* = 4, 8, 13 Hz, CH-10''), 0.95 (9H, t, *J* = 8 Hz, H_3C ×3), 0.64 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 208.7 (s, C-4), 110.5 (s, C-5''), 109.3 (s, C-5'), 73.3 (d, C-1''), 68.9 (d, C-1'), 64.8 (t, CH_2O), 64.7 (t, CH_2O), 64.2 (t, CH_2O), 64.0 (t, CH_2O), 59.3 (d, C-3), 51.3 (d, C-5), 47.8 (d, C-6'), 46.4 (d, C-6''), 34.7 (t, C-10'), 34.5 (t, C-10''), 29.7 (t, C-7'), 29.6 (t, C-7''), 28.5 (t, C-6), 26.92 (t, C-9' or C-9''), 26.91 (t, C-9' or C-9''), 25.5 (br t, C-2), 7.2 (q ×3, CH_3), 5.3 (t ×3, CH_2Si).

LRMS (EI), *m/z* (relative intensity): 588 ([M-18]$^+$, 0.3), 389 (19), 257 (12), 229 (100), 171 (12), 143 (11), 132 (33), 99 (70).

HRMS *m/z* calcd for $C_{27}H_{46}O_7S_3Si$ 606.2175 (588.2069 for M-H_2O), found 588.1270 (EI).

(3*S*,5*S*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-AS-TES-trans-SA)



From aldol reaction of **17-AS-TES** with **15**. See experimental procedure for compound **18-AS-TES-trans-AA**.

IR ν_{max} 3506, 1712 cm^{-1}.

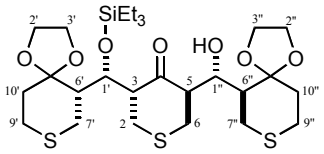
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.71 (1H, br d, *J* = 8.5 Hz, HC-1'), 4.68 (1H, dd, *J* = 2, 6 Hz, HC-1''), 4.06-3.82 (9H, m, HO, H_2CO ×4), 3.16-3.09 (2H, m, HC-2, HC-6), 2.91-2.86 (3H, m, HC-2, HC-3, HC-7'), 2.82-2.76 (4H, m, HC-5, HC-6', HC-7', HC-7''), 2.72-2.65 (3H, m, HC-9', H_2C-9''), 2.62-2.55 (2H, m, HC-7'', HC-9'), 2.18 (2H, m, HC-6', HC-10''), 2.08 (1H, ddd, *J* = 3, 6.5, 13.5 Hz, HC-10'), 2.01 (1H, ddd, *J* = 3, 8, 8.5 Hz, HC-6''), 1.83-1.77 (1H, m, HC-10''), 1.60 (1H, ddd, *J* = 3.5, 10, 13.5 Hz, HC-10'), 0.96 (9H, t, *J* = 8 Hz, H_3C ×3), 0.63 (6H, ap q, *J* = 8 Hz, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 207.5 (s, C-4), 110.7 (s, C-5''), 109.2 (s, C-5'), 69.09 (d, C-1' or C-1''), 69.05 (d, C-1' or C-1''), 64.9 (t, CH_2O), 64.5 (t, CH_2O), 64.2 (t, CH_2O), 63.9 (t, CH_2O), 59.0 (d, C-3), 51.2 (d, C-5), 48.0 (d, C-6''), 46.7 (d, C-6''), 35.1 (t, C-10'), 34.9 (t, C-10''), 29.54 (t, C-7' or C-7''), 29.47 (t, C-7' or C-7''), 26.82 (t , C-9' or C-9''), 26.80 (t, C-9' or C-9''), 25.1 (t, C-2), 23.1 (t, C-6), 7.2 (q ×3, CH_3), 5.3 (t ×3, CH_2Si).

LRMS (EI), *m/z* (relative intensity): 588 ($[M-18]^+$, 0.5), 389 (19), 257 (12), 229 (100), 171 (14), 143 (12), 132 (36), 99 (91).

HRMS *m/z* calcd for $C_{27}H_{46}O_7S_3Si$ 606.2175 (588.2069 for M-H_2O), found 588.2053 (EI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-SS-TES-trans-AA)



Following the above General Procedure, reaction of **17-SS-TES** (116 mg, 0.277 mmol) with **1** (52 mg, 0.276 mmol) for 30 min gave a crude that contained a mixture of **15**, **17-SS-TES**, **18-SS-TES-trans-AA**, and **18-SS-TES-trans-SA** (signals overlap). Fractionation of the crude by FCC (30% ethyl acetate/hexanes) gave **18-SS-TES-trans-AA** (10 mg, 6%), **18-SS-TES-trans-SA** (24 mg, 14%), and a 0.3:1.0 mixture of **18-SS-TES-trans-AA** and **18-SS-TES-trans-SA** (31 mg, 17%), respectively.

IR ν_{max} 3494, 1706 cm^{-1}.

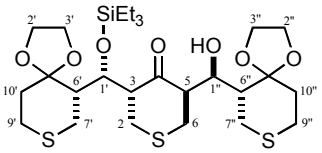
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (1H, dd, *J* = 3.5, 6.5 Hz, HC-1'), 4.36 (1H, ddd, *J* = 3.5, 4, 8 Hz, HC-1''), 4.09-3.86 (9H, m, HO, H_2CO ×4), 3.22-3.15 (2H, m, HC-3, HC-6), 3.02-2.95 (2H, m, H_2C-2), 2.95-2.87 (2H, m, HC-5, HC-7''), 2.85-2.65 (7H, m, HC-6, H_2C-7', HC-7'', HC-9', H_2C-9''), 2.47 (1H, ddd, *J* = 3, 3.5, 13.5 Hz, HC-9'), 2.28 (1H, ddd, *J* = 3, 7, 8 Hz, HC-6''), 2.17 (1H, ddd, *J* = 3.5, 8.5, 14 Hz, HC-10''), 2.06-1.98 (2H, m, HC-6', HC-10'), 1.79 (1H, ddd, *J* = 3.5, 7.5, 13.5 Hz, HC-10''), 1.63 (1H, ddd, *J* = 3.5, 13, 13.5 Hz, HC-10'), 0.94 (9H, t, *J* = 8 Hz, H_3C ×3), 0.70-0.57 (6H, m, H_2CSi ×3).

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4 (s, C-4), 110.8 (s, C-5"), 109.4 (s, C-5'), 73.4 (d, C-1"), 66.4 (d, C-1'), 64.71 (t, CH_2O), 64.66 (t, CH_2O), 64.6 (t, CH_2O), 64.1 (t, CH_2O), 57.4 (d, C-3), 54.4 (d, C-5), 49.5 (d, C-6'), 46.2 (d, C-6"), 36.7 (t, C-10'), 34.7 (t, C-10"), 31.1 (t, C-6), 30.3 (t, C-7"), 28.9 (t, C-7'), 27.3 (t, C-2), 26.8 (t, C-9"), 26.7 (t, C-9'), 7.3 (q ×3, CH_3), 5.4 (t ×3, CH_2Si).

LRMS (EI), *m/z* (relative intensity): 588 ($[M-18]^+$, 0.02), 389 (36), 257 (16), 229 (66), 191 (22), 143 (34), 132 (43), 103 (20), 99 (100).

HRMS *m/z* calcd for $C_{27}H_{46}O_7S_3Si$ 606.2175 (588.2069 for M-H_2O), found 588.2089 (EI).

(3*R*,5*R*)-*rel*-3-[(*R*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-yl(triethylsilyloxy)methyl]-5-[(*R*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-SS-TES-trans-SA)



From aldol reaction of **17-SS-TES** with **15**. See experimental procedure for compound **18-SS-TES-trans-AA**.

IR ν_{max} 3489, 1710 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72-4.69 (2H, , HC-1', HC-1"), 4.06-3.84 (9H, m, HO, H_2CO ×4), 3.30 (1H, dd, *J* = 11, 13.5 Hz, HC-6), 3.19 (1H, ddd, *J* = 2, 7.5, 9 Hz, HC-3), 3.05-2.96 (2H, m, H_2C-2), 2.82-2.65 (H, m, HC-5, H_2C-7', HC-7", HC-9', H_2C-9"), 2.57 (2H, dd, *J* = 5.5, 13.5 Hz, HC-6, HC-7"), 2.49 (1H, br d, *J* = 13.5 Hz, HC-9'), 2.23-2.17 (1H, m, HC-10'), 2.05 (1H, ddd, *J* = 4, 7.5, 11 Hz, HC-6'), 1.99 (1H, ddd, *J* = 3, 4, 13.5 Hz, HC-10"), 1.94 (1H, ddd, *J* = 3, 7.5, 8.5 Hz, HC-6"), 1.83-1.77 (1H, m, HC-10'), 1.66 (1H, ddd, *J* = 4, 13, 13 Hz, HC-10"), 0.92 (9H, ap t, *J* = 8 Hz, H_3C ×3), 0.68-0.57 (6H, m, H_2CSi ×3).

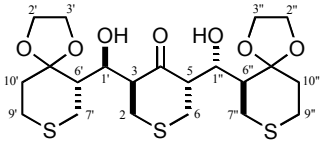
^{13}C NMR (125 MHz, $CDCl_3$) δ 210.7 (s, C-4), 110.7 (s, C-5"), 109.5 (s, C-5'), 70.6 (d, C-1"), 66.8 (d, C-1'), 64.90 (t, CH_2O), 64.85 (t, CH_2O), 64.7 (t, CH_2O), 64.2 (t, CH_2O), 56.5 (d, C-3), 53.6 (d, C-5), 49.5 (d, C-6'), 46.4 (d, C-6"), 36.7 (t, C-10'), 34.7 (t, C-10"), 29.4 (t, C-7"), 29.2 (t,

C-7'), 26.8 (t, C-9''), 26.7 (t, C-9'), 23.6 (t, C-2 or C-6), 23.5 (t, C-2 or C-6), 7.3 (q ×3, CH_3), 5.4 (t ×3, CH_2Si).

LRMS (EI), *m/z* (relative intensity): 577 ($[M-29]^+$, 0.6), 389 (37), 257 (17), 229 (69), 201 (18), 191 (24), 143 (35), 132 (42), 99 (100).

HRMS *m/z* calcd for $C_{27}H_{46}O_7S_3Si$ 606.2175 (577.1784 for $M-C_2H_5$), found 577.1798 (EI).

(3*S*,5*S*)-*rel*-3,5-Bis[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxmethyl]tetrahydro-4*H*-thiopyran-4-one (18-SA-trans-SA)



Following the General Procedure for MOM deprotection, **18-SA-MOM-trans-SA** (9 mg, 0.017 mmol) gave the titled compound (3 mg , 35%) and recovered **18-SA-MOM-trans-SA** (5 mg, 55%) after fractionation by PTLC (80% Ethyl acetate/hexanes). Following the General Procedure for TES deprotection, treatment of **18-SA-TES-trans-SA** (7 mg, 0.012 mmol) with HF·pyridine/THF (0.40 mL) for 48 h gave the titled compound (5 mg , 90%) after fractionation by PTLC (30% Ethyl acetate/hexanes).

IR ν_{max} 3483, 1708 cm^{-1}.

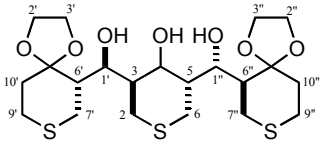
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (2H, br d, *J* = 8 Hz, HC-1'/HC-1''), 4.07-3.95 (8H, m, H_2CO ×4), 3.86 (2H, br s, HO), 3.24 (2H, dd, *J* = 10.5, 13 Hz, HC-2/HC-6), 2.94 (2H, ddd, *J* = 3, 6, 10.5 Hz, HC-3/HC-5), 2.88 (2H, dd, *J* = 6, 13 Hz, HC-2/HC-6), 2.80-2.67 (6H, m, HC-7'/7'', H_2C-9'/9''), 2.63 (2H, dd, *J* = 8, 14 Hz, HC-7'/7''), 2.18 (2H, dd, *J* = 3.5, 7.5, 13.5 Hz, HC-10'/10''), 2.02 (2H, ddd, *J* = 3.5, 8, 8 Hz, HC-6', HC-6''), 1.80 (2H, ddd, *J* = 3.5, 8.5, 13.5 Hz, HC-10', HC-10'').

^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7 (s, C-4), 110.6 (s ×2, C-5'/5''), 70.2 (d ×2, C-1'/1''), 64.9 (t ×2, CH_2O), 64.2 (t ×2, CH_2O), 52.9 (d ×2, C-3/5), 47.3 (d ×2, C-6'/6''), 35.2 (t ×2, C-10'/10''), 29.5 (t ×2, C-7'/7''), 26.8 (t ×2, C-9'/9''), 24.7 (t ×2, C-2/6).

LRMS (EI), *m/z* (relative intensity): 474 ([M-18]$^+$, 0.3), 456 (2), 304 (5), 188 (11), 159 (5), 132 (68), 115 (6), 99 (100).

HRMS *m/z* calcd for $C_{21}H_{32}O_7S_3$ 492.1310 (474.1205 for M-H_2O), found 474.1196 (EI).

(3*S*,5*S*)-*rel*-3,5-Bis[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-2*H*-thiopyran-4-ol (190)



Following the General Procedure for the $NaBH_4$, reduction of **18-SA-trans-SA** (18 mg, 0.037 mmol) gave the titled compound **190** (8 mg, 40%) as a colourless solid after fractionation by PTLC (ethyl acetate).

IR ν_{max} 3455 cm^{-1}.

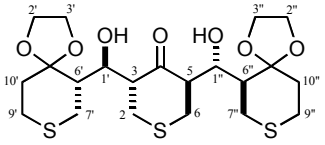
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (1H, s, HOC-4), 4.39 (1H, s, HO-C-1"), 4.34-4.31 (2H, m, HC-1', HC-1"), 4.17 (1H, br s, HC-4), 4.07-3.97 (8H, m, H_2CO ×4), 3.79 (1H, d, *J* = 5 Hz, HOC-1'), 3.21 (1H, dd, *J* = 12, 12.5 Hz, HC-6), 3.12 (1H, dd, *J* = 4, 13.5 Hz, HC-2), 2.93 (1H, dd, *J* = 8.5, 14 Hz, HC-7'), 2.88-2.80 (2H, m, HC-7', HC-7"), 2.79-2.63 (5H, m, HC-2, H_2C-9', H_2C-9"), 2.60 (1H, dd, *J* = 7, 14 Hz, HC-7"), 2.24-2.05 (6H, m, HC-3, HC-5, HC-6, HC-6", HC-10', HC-10"), 2.01 (1H, ddd, *J* = 3, 6.5, 9 Hz, HC-6'), 1.83 (1H, ddd, *J* = 3.5, 7, 13.5 Hz, HC-10"), 1.79 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-10').

^{13}C NMR (125 MHz, $CDCl_3$) δ 111.2 (s, C-5'), 110.9 (s, C-5"), 76.0 (d, C-1"), 73.4 (d, C-4), 72.5 (d, C-1'), 64.9 (t, CH_2O), 64.4 (t, CH_2O), 64.3 (t, CH_2O), 64.1 (t, CH_2O), 46.23 (d, C-6'), 46.16 (d, C-6'), 44.9 (d, C-3), 38.4 (d, C-5), 35.7 (t, C-10'), 34.3 (t, C-10"), 31.3 (t, C-7'), 29.2 (t, C-7"), 26.9 (t, C-9' or C-9"), 26.8 (t, C-9' or C-9"), 23.4 (t, C-2), 20.0 (t, C-6).

LRMS (EI), *m/z* (relative intensity): 494 ([M]$^+$, 36), 476 (27), 458 (52), 432 (23), 414 (32), 273 (25), 132 (53), 99 (100).

HRMS *m/z* calcd for $C_{21}H_{34}O_7S_3$ 494.1467, found 494.1459 (EI).

(3*R*,5*R*)-*rel*-3,5-Bis[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-AA-trans-AA)



Following the General Procedure for TES deprotection, treatment of **18-AA-TES-trans-AA** (46 mg, 0.076 mmol) with HF·pyridine/THF (0.83 mL) for 21 h gave the titled compound (44 mg, quantitative yield) as a colourless solid after fractionation by FCC (30-50% ethyl acetate/hexane).

IR ν_{max} 3487, 1708 cm^{-1}.

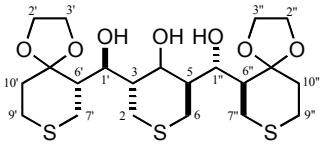
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.24 (2H, ddd, *J* = 3, 3.5, 8 Hz, HC-1'/HC-1"), 4.08-3.94 (10H, m, H_2CO ×4, HO ×2), 3.27 (2H, dd, *J* = 10, 13 Hz, HC-2/HC-6), 3.08 (2H, ddd, *J* = 3.5, 5.5, 10 Hz, HC-3/HC-5), 2.96 (2H, dd, *J* = 3, 14 Hz, HC-7'/HC-7"), 2.91 (2H, dd, *J* = 5.5, 13 Hz, HC-2/HC-6), 2.80-2.73 (4H, m, HC-7'/HC-7", HC-9'/HC-9"), 2.68-2.64 (2H, m, HC-9'/HC-9"), 2.34 (2H, ddd, *J* = 3, 7, 8 Hz, HC-6'/HC-6"), 2.15 (2H, ddd, *J* = 3.5, 9, 13.5 Hz, HC-10'/HC-10"), 1.80 (2H, ddd, *J* = 3, 7, 13.5 Hz, HC-10'/HC-10").

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0 (s, C-4), 110.7 (s ×2, C-5'/5'), 72.7 (d ×2, C-1'/1"), 64.9 (t ×2, CH_2O), 64.2 (t ×2, CH_2O), 52.8 (d ×2, C-3/5), 46.6 (d ×2, C-6'/6"), 34.5 (t ×2, C-10'/10"), 30.5 (t ×2, C-2/6), 29.7 (t ×2, C-7'/7"), 26.9 (t ×2, C-9'/9").

LRMS (EI), *m/z* (relative intensity): 492 ($[M]^+$, 0.1), 474 (0.7), 456 (0.3), 304 (13), 286 (10), 188 (31), 159 (24), 132 (100), 99 (81).

HRMS *m/z* calcd for $C_{21}H_{32}O_7S_3$ 492.1310, found 492.1317 (EI).

(3*R*,5*R*)-*rel*-3,5-Bis[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-tetrahydro-2*H*-thiopyran-4-ol (191)



Following the General Procedure for the $NaBH_4$, reduction of **18-AA-trans-AA** (22 mg, 0.045 mmol) gave the titled compound **191** (20 mg, 89%) as a colourless solid after fractionation by FCC (75% ethyl acetate in hexanes).

IR ν_{max} 3440 cm^{-1}.

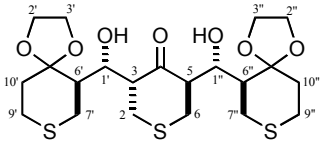
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (1H, d, *J* = 1 Hz, HO), 4.47 (1H, br d, *J* = 2.5 Hz, HO), 4.45 (1H, s), 4.33 (1H, ddd, *J* = 4.5, 5, 8 Hz), 4.24 (1H, dd, *J* = 2, 9 Hz), 4.05-3.96 (8H, m, H_2CO ×4), 3.73 (1H, d, *J* = 4.5 Hz, HO), 3.38 (1H, dd, *J* = 12.5, 12.5 Hz), 3.29-3.27 (1H, m), 3.01 (1H, dd, *J* = 3, 14 Hz), 2.93-2.64 (8H, m), 2.30-2.12 (8H, m), 1.83 (1H, ddd, *J* = 4, 7.5, 13.5 Hz), 1.76 (1H, ddd, *J* = 4, 8.5, 13.5 Hz).

^{13}C NMR (125 MHz, $CDCl_3$) δ 111.2 (s), 111.1 (s), 76.2 (d), 73.0 (d), 66.4 (d), 64.9 (t), 64.4 (t), 64.2 (t), 64.0 (t), 47.1 (d), 46.4 (d), 43.7 (d), 37.0 (d), 35.6 (t), 34.5 (t), 31.2 (t), 28.3 (t), 26.9 (t), 26.7 (t), 25.9 (t), 25.8 (t).

LRMS (EI), *m/z* (relative intensity): 494 ($[M]^+$, 12), 476 (7), 458 (17), 273 (19), 189 (14), 161 (21), 132 (72), 99 (100).

HRMS *m/z* calcd for $C_{21}H_{34}O_7S_3$ 494.1467, found 494.1473 (EI).

(3*R*,5*R*)-*rel*-3-[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*R*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-AA-trans-SA)



Following the General Procedure for MOM deprotection, **18-SA-MOM-trans-AA** (11 mg, 0.0205 mmol) gave the titled compound (6 mg, 55%) and recovered **18-SA-MOM-trans-AA** (4 mg, 40%) after fractionation by PTLC (80% Ethyl acetate/hexanes). Following the General Procedure for TES deprotection, treatment of **18-AA-TES-trans-SA** (39 mg, 0.064 mmol) with HF·pyridine/THF (0.81 mL) for 21 h gave the titled compound (22 mg, 68%) after fractionation by PTLC (75% Ethyl acetate/hexanes). Similar treatment of **18-SA-TES-trans-AA**

(64 mg, 0.11 mmol) with HF·pyridine/THF (1.0 mL) for 48 h gave the titled compound (37 mg, 71%) after fractionation by PTLC (75% Ethyl acetate/hexanes).

IR ν_{max} 3480, 1708 cm^{-1}.

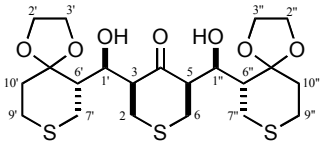
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.59 (1H, br dd, *J* = 2, 8.5 Hz, HC-1"), 4.26 (1H, ddd, *J* = 3, 3.5, 8 Hz, HC-1'), 4.09-3.97 (8H, m, H_2CO ×4), 3.96 (1H, s, HOC-1'), 3.88 (1H, d, *J* = 3 Hz, HOC-1"), 3.28-3.23 (2H, m, HC-2, HC-6), 3.09 (1H, ddd, *J* = 3.5, 6, 9.5 Hz, HC-3), 2.99 (1H, dd, *J* = 6, 12.5 Hz, HC-2), 2.96 (1H, dd, *J* = 3, 14 Hz, HC-7'), 2.93-2.89 (1H, m, HC-5), 2.82-2.64 (7H, m, HC-6. HC-7', HC-7", H_2C-9', H_2C-9"), 2.60 (1H, dd, *J* = 8, 14 Hz, HC-7"), 2.36 (1H, ddd, *J* = 3, 7, 8 Hz, HC-6'), 2.20-2.13 (2H, m, HC-10', HC-10"), 2.00 (1H, ddd, *J* = 3, 8.5, 8.5 Hz, HC-6"), 1.82-1.77 (2H, m, HC-10', HC-10").

^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1 (s, C-4), 110.6 (s ×2, C-5', C-5'"), 72.6 (d, C-1'), 70.4 (d, C-1"), 64.89 (t, CH_2O), 64.84 (t, CH_2O), 64.23 (t, CH_2O), 64.22 (t, CH_2O), 53.6 (d, C-5), 51.6 (d, C-3), 47.3 (d, C-6"), 46.1 (d, C-6'), 35.1 (t, C-10"), 34.3 (t, C-10'), 29.9 (t, C-7'), 29.4 (t, C-7"), 28.9 (t, C-2), 27.0 (t, C-9'), 26.8 (t, C-9"), 25.0 (t, C-6).

LRMS (EI), *m/z* (relative intensity): 492 ($[M]^+$, 0.1), 474 (0.3), 456 (0.8), 188 (14), 159 (5), 132 (32), 99 (100), 86 (27).

HRMS *m/z* calcd for $C_{21}H_{32}O_7S_3$ 492.1310, found 492.1304 (EI).

(3S,5R)-*rel*-3-[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxmethyl]-5-[(*R*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-SA-cis-SA)



Isomerization of **18-AA-trans-SA** (16 mg, 0.033 mmol) for 3 d according to the general procedure gave a 46:43:11 mixture (by ^{1}H NMR) of **18-AA-trans-SA**, **18-SA-cis-SA**, and **18-AA-cis-AA**, respectively (14 mg), after work up. Fractionation by PTLC (ethyl acetate; multiple elutions) gave **18-AA-trans-SA** (6 mg, 37%), and a 5:1 mixture of **18-SA-cis-SA** and **18-AA-**

cis-AA, respectively (7 mg, 47%). The latter mixture was fractionated by PTLC (2% MeOH in CH_2Cl_2; multiple elutions) to give **18-SA-cis-SA** (4 mg, 23%) and **18-AA-cis-AA** (2 mg, 13%).

IR ν_{max} 3489, 1702 cm^{-1}.

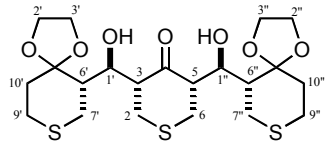
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (2H, ?, HC-1'/HC-1"), 4.08-3.98 (8H, m, H_2CO ×4), 3.85 (2H, d, *J* = 2.5 Hz, HO ×2), 3.09-2.98 (4H, m, HC2-2/H_2C-6), 2.92 (2H, ap ddd, *J* = 5, 5, 12 Hz, HC-3/HC-5), 2.75 (2H, ddd, *J* = 3, 9.5, 13.5 Hz, HC-9'/HC-9"), 2.75-2.67 (4H, m, H_2C-7'/H_2C-7"), 2.64 (2H, ap ddd, *J* = 3.5, 6.5, 13.5 Hz, HC-9'/HC-9"), 2.19-2.12 (4H, m, HC-6'/HC-6", HC-10'/HC-10"), 1.77 (2H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-10', HC-10").

^{13}C NMR (125 MHz, $CDCl_3$) δ 210.5 (s, C-4), 110.9 (s ×2, C-5'/5"), 70.8 (d ×2, C-1'/1"), 64.7 (t ×2, CH_2O), 64.1 (t ×2, CH_2O), 56.9 (d ×2, C-3/5), 46.9 (d ×2, C-6'/6"), 35.5 (t ×2, C-10'/10"), 31.8 (t ×2, C-2/6), 30.1 (t ×2, C-7'/7"), 26.7 (t ×2, C-9'/9").

LRMS (EI), *m/z* (relative intensity): 492 ($[M]^+$, 0.2), 474 (1), 456 (5), 304 (3), 286 (9), 188 (10), 132 (77), 99 (100).

HRMS *m/z* calcd for $C_{21}H_{32}O_7S_3$ 492.1310, found 492.1301 (EI).

(3*R*,5*S*)-*rel*-3-[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxmethyl]-5-[(*R*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-AA-cis-AA)



From the isomerization of **18-AA-trans-SA**. See experimental procedure for compound **18-SA-cis-SA**.

IR ν_{max} 3493, 1704 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$) δ 4.12 (2H, ddd, *J* = 3, 4, 7.5 Hz, HC-1', HC-1"), 4.07-3.93 (8H, m, H_2CO ×4), 3.83 (2H, d, *J* = 4 Hz, HO ×2), 3.20 (2H, dd, *J* = 13.5, 14 Hz, HC-2/HC-6), 2.89-2.85 (4H, m, HC-2/HC-6, HC-3/HC-5), 2.76-2.58 (6H, m, HC-7'/HC-7", H_2C-9'/H_2C-9"), 2.48 (2H,

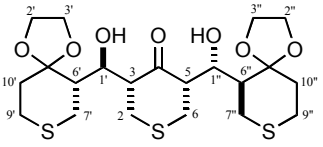
dd, *J* = 7.5, 13.5 Hz, HC-7'/HC-7"), 2.43 (2H, ddd, *J* = 3, 7.5, 7.5 Hz, HC-6'/HC-6"), 2.12 (2H, ddd, *J* = 3.5, 8.5, 13.5 Hz, HC-10'/10"), 1.75 (2H, ddd, *J* = 3.5, 8, 13.5 Hz, HC-10'/10").

^{13}C NMR (150 MHz, $CDCl_3$) δ 210.4 (s, C-4), 110.3 (s ×2, C-5'/5"), 72.4 (d ×2, C-1'/1"), 64.6 (t ×2, CH_2O), 64.1 (t ×2, CH_2O), 56.2 (d ×2, C-3/5), 46.6 (d ×2, C-6'/6"), 34.6 (t ×2, C-10'/10"), 34.4 (t ×2, C-2/6), 30.1 (t ×2, C-7'/7), 26.7 (t ×2, C-9'/9").

LRMS (EI), *m/z* (relative intensity): 474 ($M-18^+$, 0.4).

HRMS *m/z* calcd for $C_{21}H_{32}O_7S_3$ 492.1310 (474.1205 for $M-H_2O$), found 474.1209 (EI).

(3*R*,5*S*)-*rel*-3,5-Bis[(*S*)-(6*S*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxmethyl]tetrahydro-4*H*-thiopyran-4-one (18-AA-cis-SA)



Isomerization of **18-AA-trans-AA** (12mg, 0.024 mmol) for 3 d according to the general procedure gave a 46:29:25 mixture (by ^{1}H NMR) of **18-AA-cis-SA**, **18-SA-trans-SA**, and **18-AA-trans-AA**, respectively (12 mg), after work up. Fractionation by PTLC (75% ethyl acetate in hexane; multiple elutions) gave a mixture of **18-SA-trans-SA** and **18-AA-trans-AA** (6 mg, 50%) and **18-AA-cis-SA** (6 mg, 50%).

IR ν_{max} 3491, 1705 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.37 (1H, ddd, *J* = 4, 5, 6 Hz, HC-1"), 4.15 (1H, ddd, *J* = 3, 4, 8 Hz, HC-1'), 4.10-3.95 (8H, m, H_2CO ×4), 3.84 (1H, d, *J* = 4 Hz, HOC-1'), 3.69 (1H, d, *J* = 4 Hz, HOC-1"), 3.30 (1H, dd, *J* = 13, 14 Hz, HC-2), 3.06-2.98 (2H, m, H_2C-6), 2.95-2.89 (3H, m, HC-2, HC-3, HC-5), 2.85-2.60 (7H, m, HC-7', H_2C-7", H_2C-9', H_2C-9"), 2.55 (1H, dd, *J* = 7, 14 Hz, HC-7'), 2.49 (1H, ddd, *J* = 3, 7, 8 Hz, HC-6'), 2.24-2.13 (3H, m, HC-6", HC-10', HC-10"), 1.80 (1H, ddd, *J* = 3.5, 7.5, 13.5 Hz, HC-10'), 1.74 (1H, ddd, *J* = 3.5, 9.5, 13.5 Hz, HC-10").

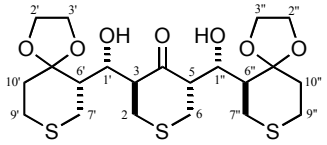
^{13}C NMR (125 MHz, $CDCl_3$) δ 210.5 (s, C-4), 111.1 (s, C-5"), 110.4 (s, C-5'), 72.9 (d, C-1'), 71.0 (d, C-1"), 64.9 (t, CH_2O), 64.5 (t, CH_2O), 64.3 (t, CH_2O), 63.8 (t, CH_2O), 57.8 (d, C-5), 55.6

(d, C-3), 46.6 (d, C-6'), 45.8 (d, C-6''), 35.3 (t, C-10''), 34.9 (t, C-2), 34.7 (t, C-10'), 32.2 (t, C-6), 30.3 (t, C-7''), 30.0 (t, C-7'), 26.9 (t, C-9'), 26.7 (t, C-9'').

LRMS (EI), *m/z* (relative intensity): 492 ($[M]^+$, 0.1), 474 (0.4), 456 (0.7), 304 (6), 286 (7), 188 (15), 132 (74), 99 (100).

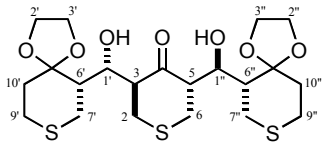
HRMS *m/z* calcd for $C_{21}H_{32}O_7S_3$ 492.1310, found 492.1319 (EI).

(3*S*,5*S*)-*rel*-3-[(*S*)-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*R*)-(6*R*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-AS-trans-AA)



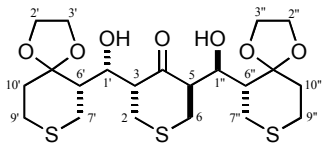
Following the General Procedure for TES deprotection, treatment of **18-AS-TES-trans-SA** (10 mg, 0.017 mmol) with HF·pyridine/THF (0.50 mL) for 24 h gave the titled compound (9 mg, quantitative yield).

(3*S*,5*S*)-*rel*-3-[(*S*)-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-AS-trans-AA)



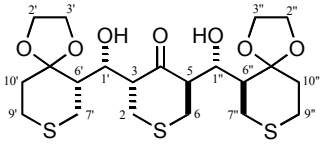
Following the General Procedure for TES deprotection, treatment of **18-AS-TES-trans-AA** (5 mg, 0.0083 mmol) with HF·pyridine/THF (0.25 mL) for 24 h gave the titled compound (6 mg, quantitative yield).

(3*R*,5*R*)-*rel*-3-[(*S*)-(6*R*)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(*S*)-(6*S*)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-SS-trans-SA)



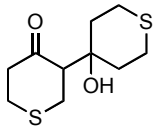
Following the General Procedure for TES deprotection, treatment of **18-SS-TES-trans-SA** (24 mg, 0.040 mmol) with HF·pyridine/THF (0.60 mL) for 24 h gave the titled compound (19 mg, quantitative yield).

(3*R*,5*R*)-*rel*-3-[(*S*)-(6R)-1,4-Dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]-5-[(R)-(6R)-1,4-dioxa-8-thiaspiro[4.5]dec-6-ylhydroxymethyl]tetrahydro-4*H*-thiopyran-4-one (18-SS-trans-AA)



Following the General Procedure for TES deprotection, treatment of **18-SS-TES-trans-AA** (10 mg, 0.017 mmol) with HF·pyridine/THF (0.50 mL) for 4 h gave the titled compound (8 mg, quantitative yield).

3-(4-hydroxytetrahydro-4*H*-thiopyran-4-yl)tetrahydro-4*H*-thiopyran-4-one



$MgBr_2 \cdot OEt_2$ (2 equiv) was added to a stirred solution of thiopyranone **16** (1 equiv, 121 mg, 1.04 mmol, 0.3 M in CH_2Cl_2) at room temperature under Ar. After 10 min, *i*-Pr_2NEt (1 equiv) was added. The reaction mixture was allowed to stir for 10 min and then was quenched by the addition of water with vigorous stirring. The mixture was diluted with ethyl acetate and transferred to a separatory funnel containing saturated Na_2CO_3 solution with ethyl acetate. The organic layer was removed and the aqueous layer was washed with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated to give the crude products. Analysis by ^1H NMR revealed a 1:13 ratio of **16** and **182**, respectively (93% conv.). Fractionation of the crude by FCC (10% ethyl acetate/hexanes) gave **182** (110 mg, 91%).

IR (DRIFT) ν_{max}: 3503, 1696, 1424, 1279 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.65 (1H, br s, HO), 3.12-2.85 (6H, m, H_2C-2, HC-2', H_2C-6, HC-6'), 2.75-2.68 (3H, m, HC-3, H_2C-5), 2.38-2.30 (2H, m, HC-2', HC-6'), 2.04 (1H, br d, J = 13.5 Hz) and 1.94 (1H, br d, J = 13.5 Hz) (HC-3', HC-5'), 1.74 (1H, ddd, J = 2.5, 12, 13.5 Hz) and 1.59 (1H, ddd, J = 3, 12.5, 13.5 Hz) (HC-3', HC-5').

^{13}C NMR (125 MHz, $CDCl_3$) δ: 213.1 (C-4), 71.2 (C-4'), 61.8 (C-3), 46.0 (C-5), 37.1 (C-3' or C-5'), 34.7 (C-3' or C-5'), 31.4 (C-2 or C-4), 30.9 (C-2 or C-6), 23.6 (C-2' or C-6'), 23.5 (C-2' or C-6').

LRMS (CI, NH_3), *m/z* (relative intensity): 250 ($[M+18]^+$, 15), 233 ($[M+1]^+$, 100), 215 (32), 116 (14).

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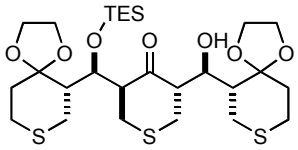
6. APPENDIX

Appendix A. Crystallographic data for 18-SA-TES-trans-AA



18-SA-TES-trans-AA

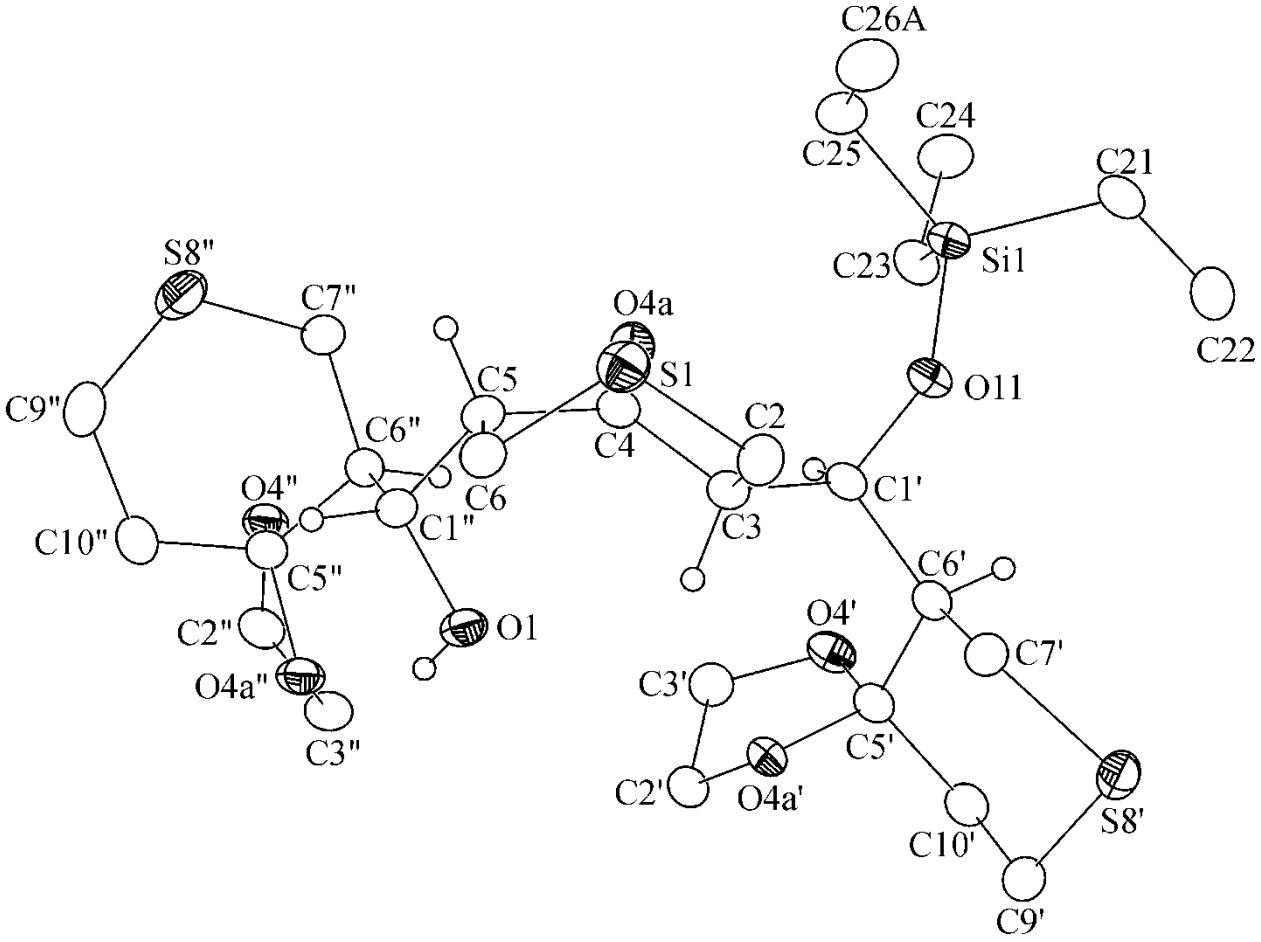


Figure A-1. ORTEP plot of **18-SA-TES-trans-AA**.

Table A-1. Crystal data and structure refinement for **18-SA-TES-trans-AA**.

Empirical formula	C27.86 H47.29 N0.43 O7 S3 Si	
Formula weight	624.56	
Temperature	173(2) K	
Wavelength	1.54184 Å	
Crystal system	Monoclinic	
Space group	P 21/n	
Unit cell dimensions	a = 14.0686(7) Å	α= 90°.
	b = 10.7894(5) Å	β= 107.6905(15)°.
	c = 22.0341(11) Å	γ = 90°.
Volume	3186.4(3) $Å^3$	
Z	4	
Density (calculated)	1.302 Mg/m^3	
Absorption coefficient	2.839 mm^{-1}	
F(000)	1342	
Crystal size	0.20 x 0.16 x 0.14 mm^3	
Theta range for data collection	3.33 to 65.20°.	
Index ranges	-15<=h<=16, -12<=k<=12, -25<=l<=25	
Reflections collected	20233	
Independent reflections	5345 [R(int) = 0.0538]	
Completeness to theta = 65.20°	97.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.6920 and 0.6005	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5345 / 0 / 413	
Goodness-of-fit on F^2	1.054	
Final R indices [I>2sigma(I)]	R1 = 0.0464, wR2 = 0.1334	
R indices (all data)	R1 = 0.0478, wR2 = 0.1350	
Largest diff. peak and hole	0.547 and -0.347 $e.Å^{-3}$	

Appendix B. Crystallographic data for 18-SA-MOM-trans-SA

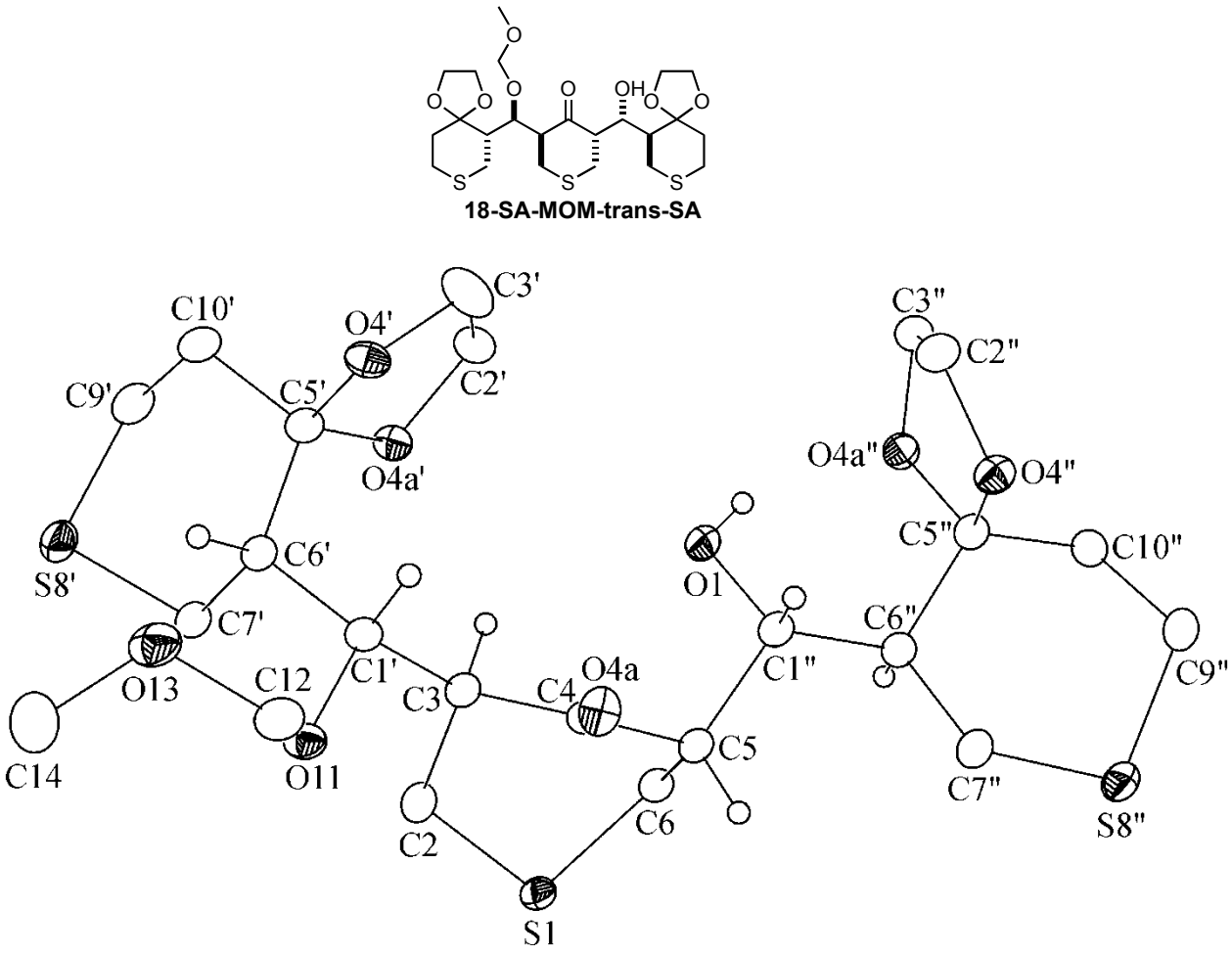


Figure B-1. ORTEP plot of **18-SA-MOM-trans-SA**.

Table B-1. Crystal data and structure refinement for **18-SA-MOM-trans-SA**

Empirical formula	C23 H36 O8 S3	
Formula weight	536.70	
Temperature	173(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 8.3983(3) Å	α= 89.6800(10)°.
	b = 11.4730(4) Å	β= 86.0480(10)°.
	c = 13.4815(4) Å	γ = 78.2380(10)°.
Volume	1268.65(7) $Å^3$	
Z	2	
Density (calculated)	1.405 Mg/m^3	
Absorption coefficient	3.064 mm^{-1}	
F(000)	572	
Crystal size	0.11 x 0.09 x 0.09 mm^3	
Theta range for data collection	3.29 to 65.08°.	
Index ranges	-9<=h<=9, -13<=k<=13, -15<=l<=15	
Reflections collected	16072	
Independent reflections	4183 [R(int) = 0.0381]	
Completeness to theta = 65.08°	96.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7722 and 0.7372	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4183 / 0 / 336	
Goodness-of-fit on F^2	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0441, wR2 = 0.1207	
R indices (all data)	R1 = 0.0446, wR2 = 0.1214	
Largest diff. peak and hole	0.422 and -0.322 $e.Å^{-3}$	